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GB A 2181346 GB 0715755 US 3963729
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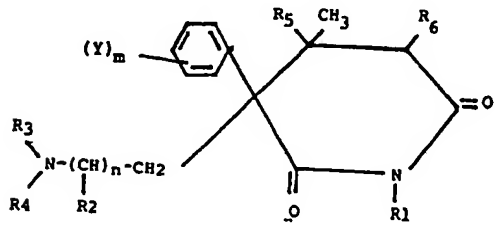
(54) Dioxopiperidine derivatives

(57) Phenyl-3-aminoalkyl-4-methyl-2,6-dioxopiperidines of the Formula



where
R1 is hydrogen or C1–C4 alkyl;
n is 1 or 2;
R2 is hydrogen or methyl, provided that one R2 is hydrogen when *n* is 2;
R3 is hydrogen or C1–C2 alkyl;
R4 is C1–C2 alkyl;
R5 and R6 are hydrogen or methyl;
m is 0 to 3; and
each Y is in a meta or para position and is hydroxy, C_1–C_2 alkoxy, C1–C2 alkyl, C1–C2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,
and pharmacologically acceptable salts thereof have anxiolytic activity.

GB 2 196 251 A

The drawing(s) originally filed was/were informal and the print here reproduced is taken from a later filed formal copy.

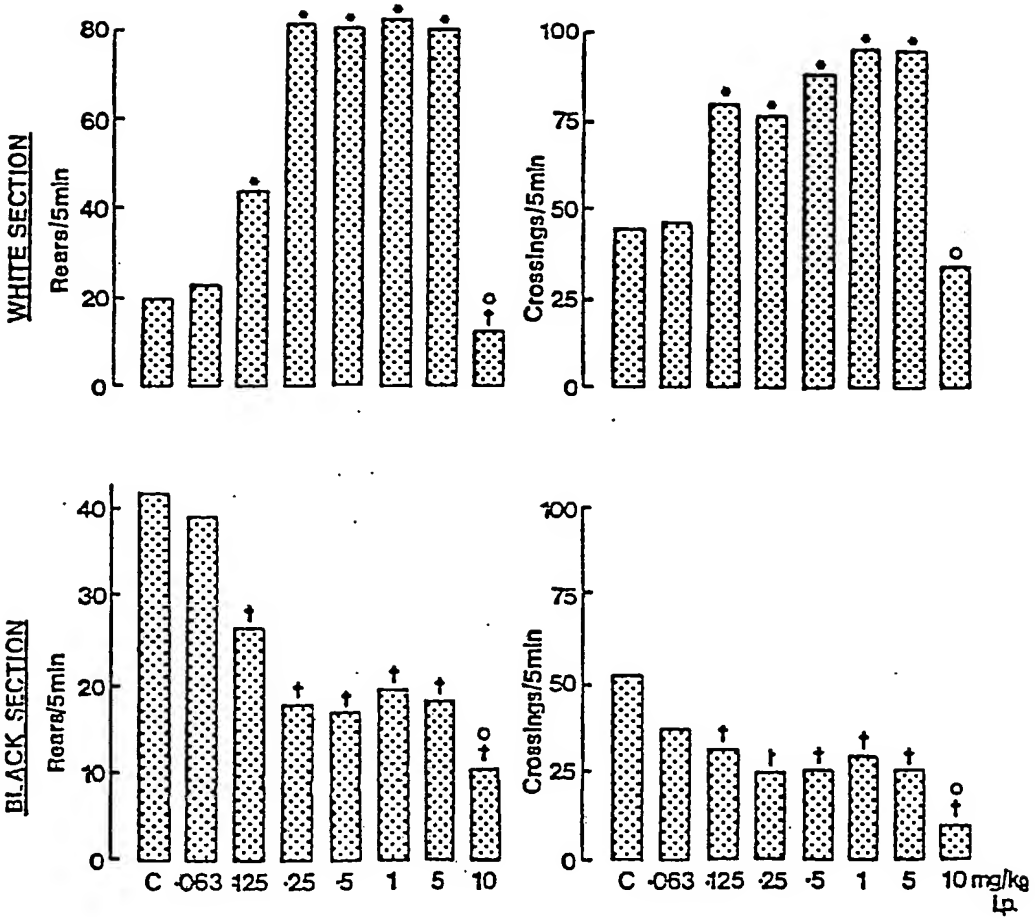

WHITE SECTION
Rears/5min
Crossings/5min
BLACK SECTION
Rears/5min
Crossings/5min
C
·063
·125
·25
·5
1
5
10
mg/kg
i.p.

FIG. 1

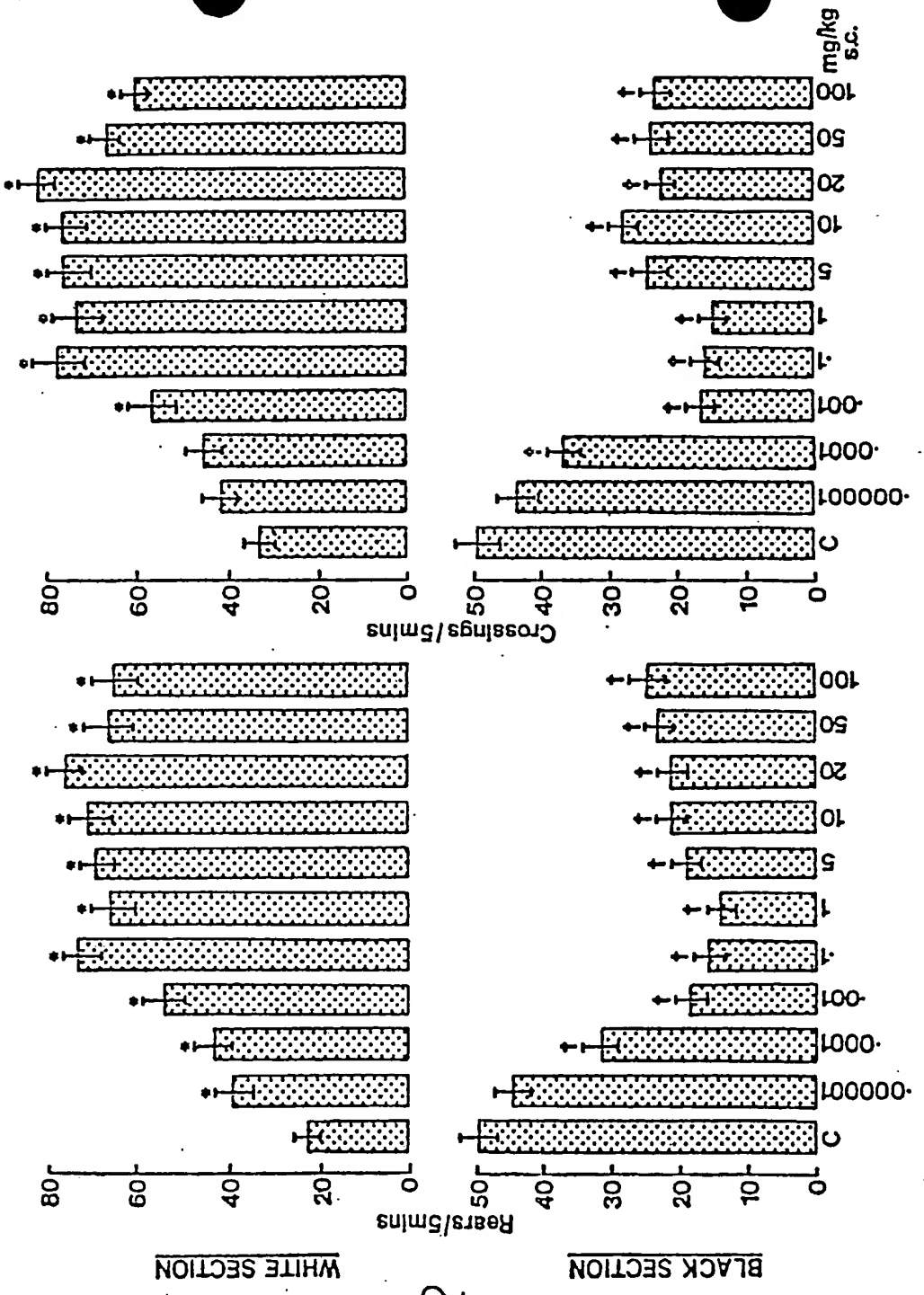

mg/kg s.c.
100
50
20
10
5
1
·1
·01
·001
·0001
·00001
C
0
10
20
30
40
50
Crossings/5mins
0
20
40
60
80
BLACK SECTION
WHITE SECTION
Rears/5mins

FIG.2

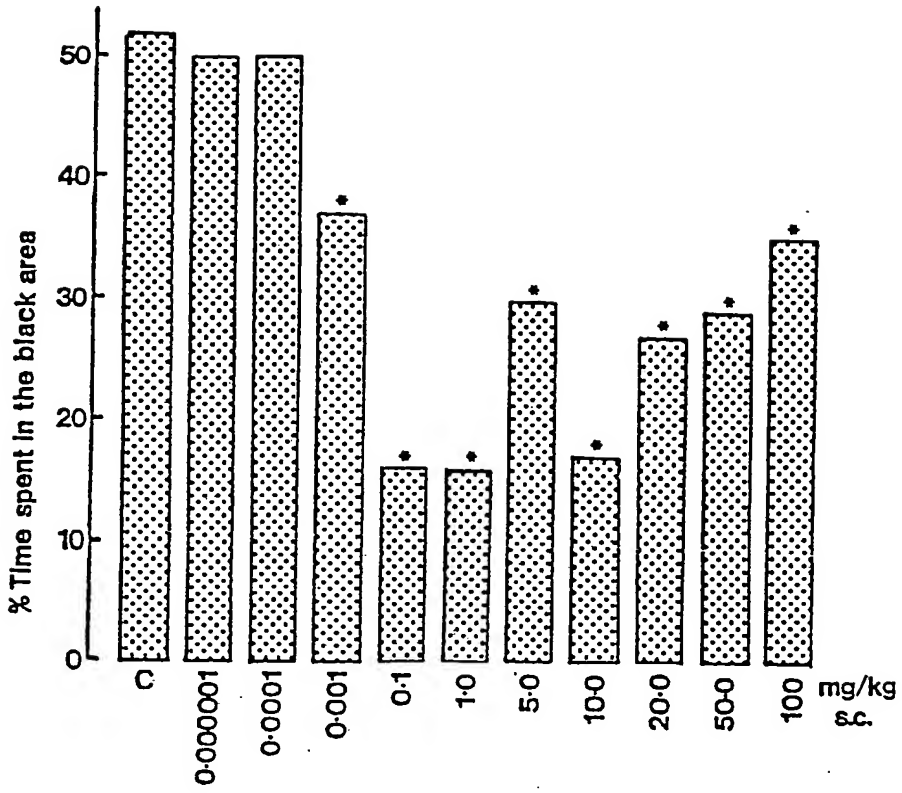

% Time spent in the black area
0
10
20
30
40
50
C
0·000001
0·0001
0·001
0·1
1·0
5·0
10·0
20·0
50·0
100
mg/kg
s.c.

FIG.3

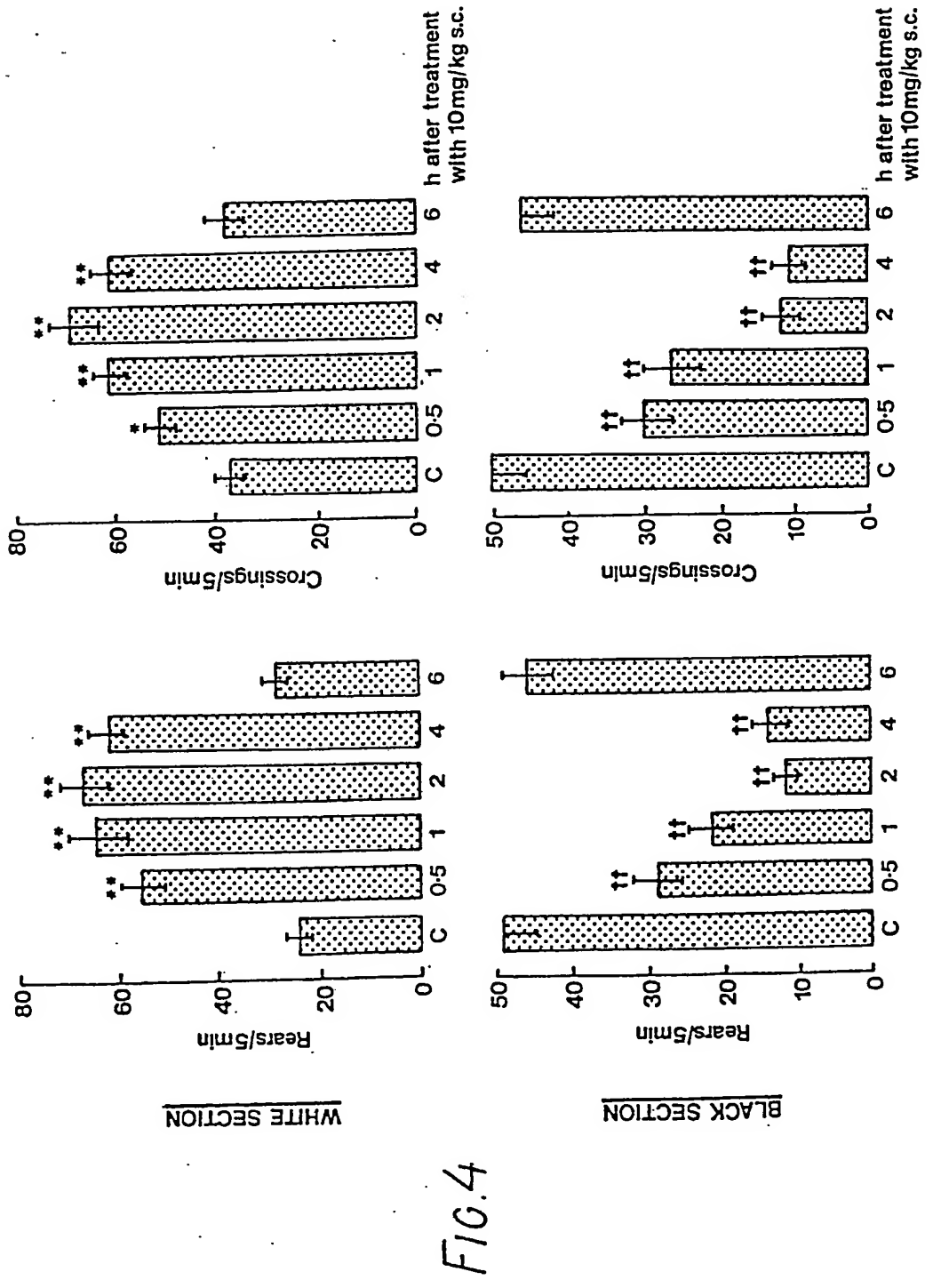

WHITE SECTION
BLACK SECTION
Crossings/5min
Rears/5min
h after treatment with 10mg/kg s.c.
C
0·5
1
2
4
6
0
20
40
60
80
10
30
50
**
††

FIG. 4

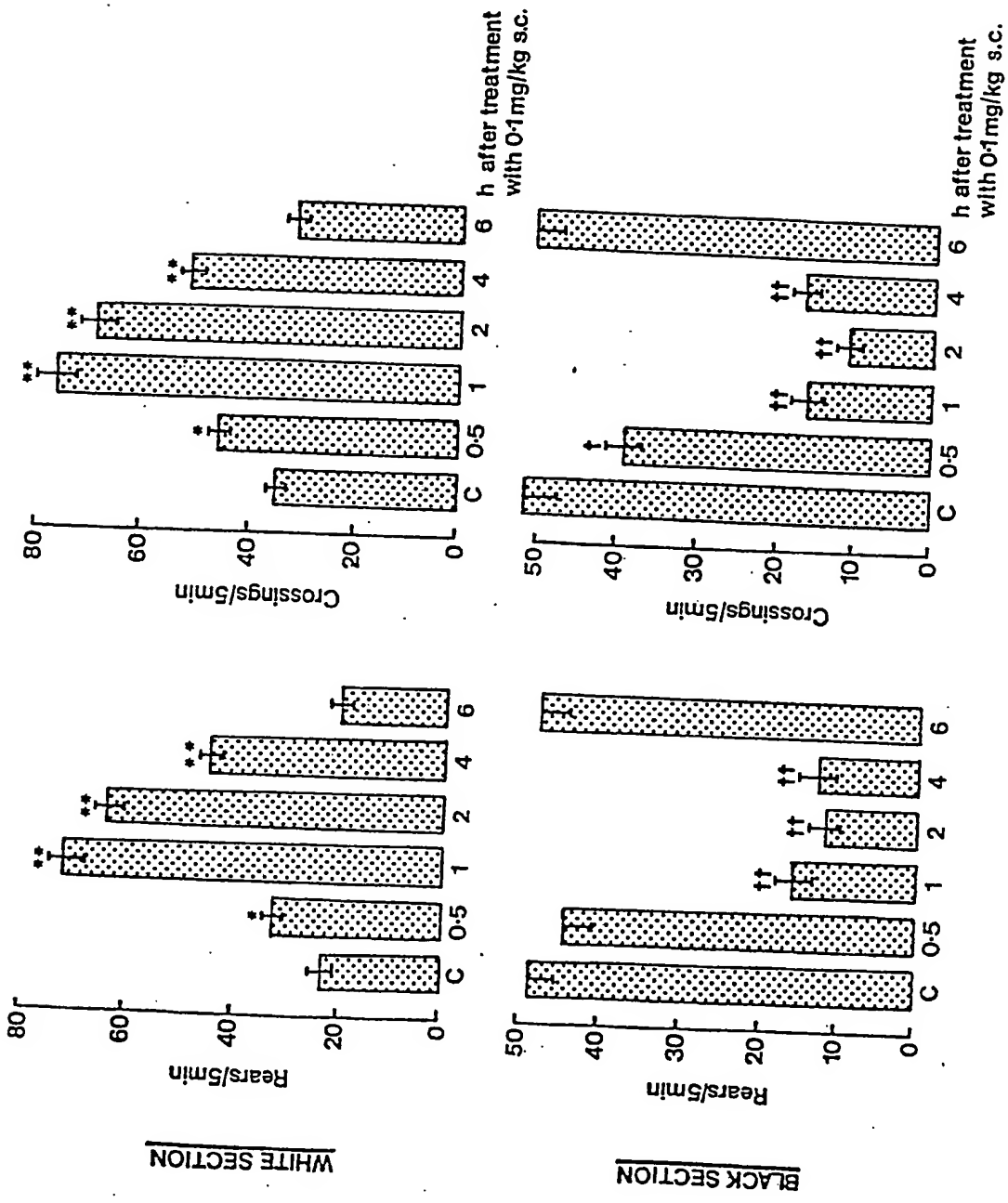

BLACK SECTION
WHITE SECTION
Rears/5min
Crossings/5min
C
0·5
1
2
4
6
h after treatment with 0·1mg/kg s.c.

FIG.5

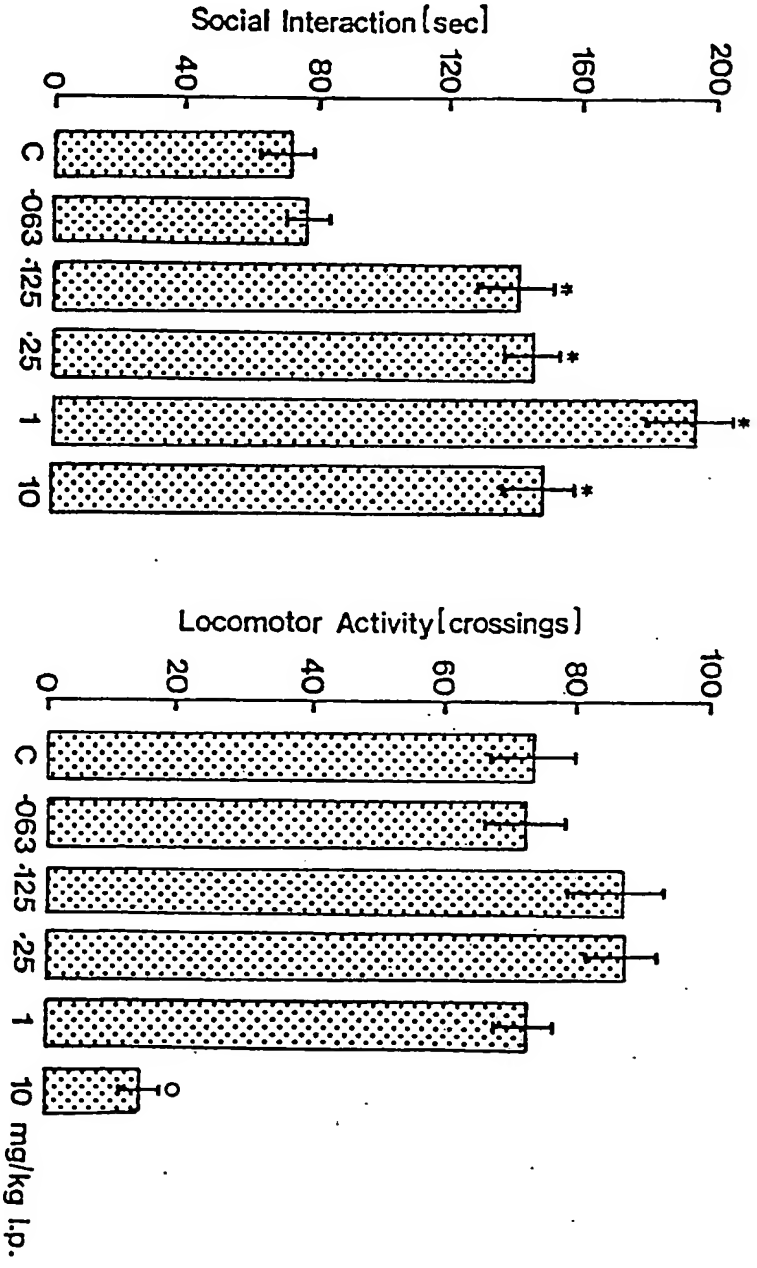

Social Interaction [sec]
0
40
80
120
160
200
C
.063
.125
.25
1
10
*
Locomotor Activity [crossings]
0
20
40
60
80
100
C
.063
.125
.25
1
10 mg/kg i.p.
o

FIG. 6

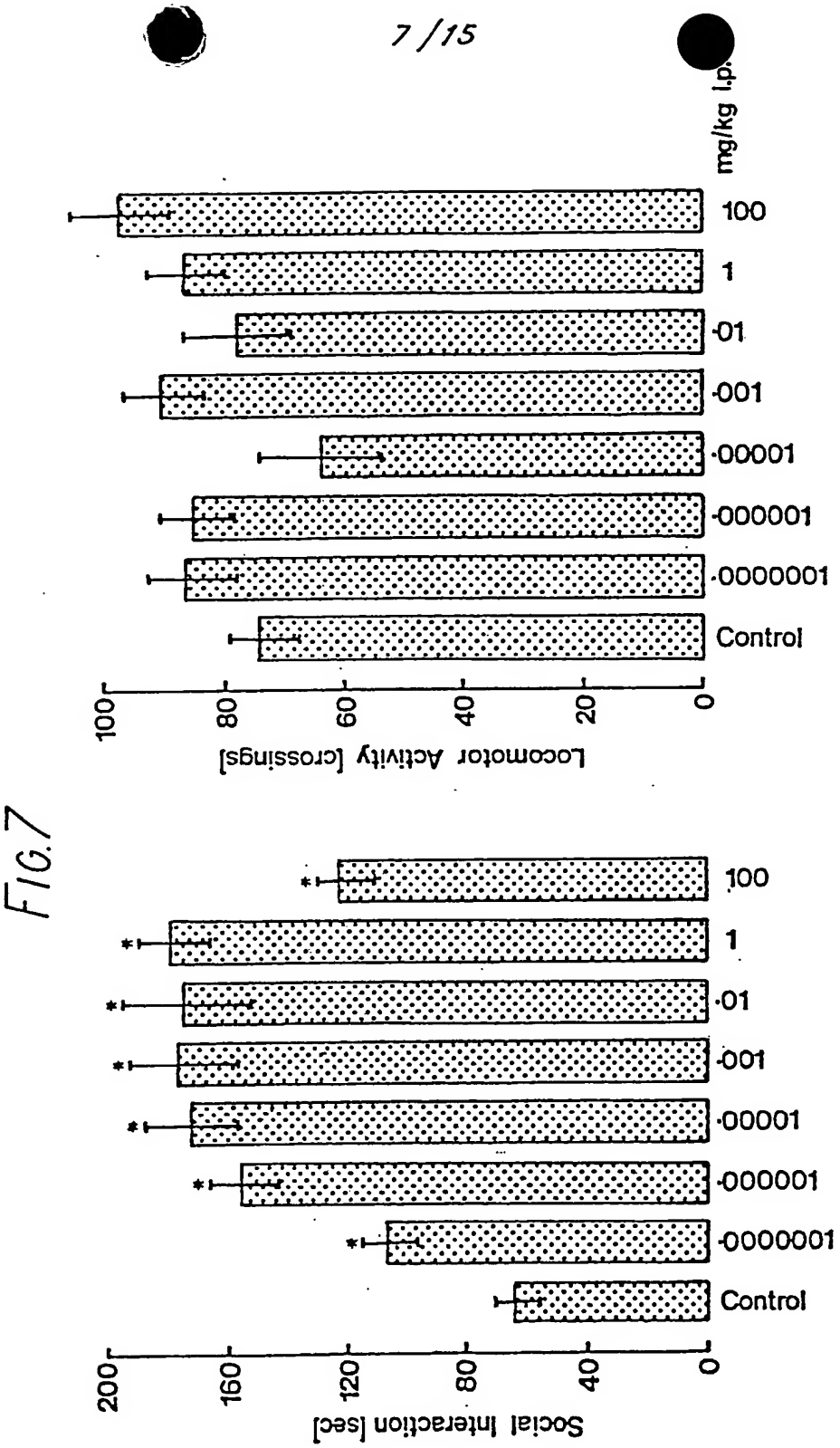

mg/kg i.p.
100
1
·01
·001
·00001
·000001
·0000001
Control
100
80
60
40
20
0
Locomotor Activity [crossings]
100
1
·01
·001
·00001
·000001
·0000001
Control
200
160
120
80
40
0
Social Interaction [sec]

FIG.7

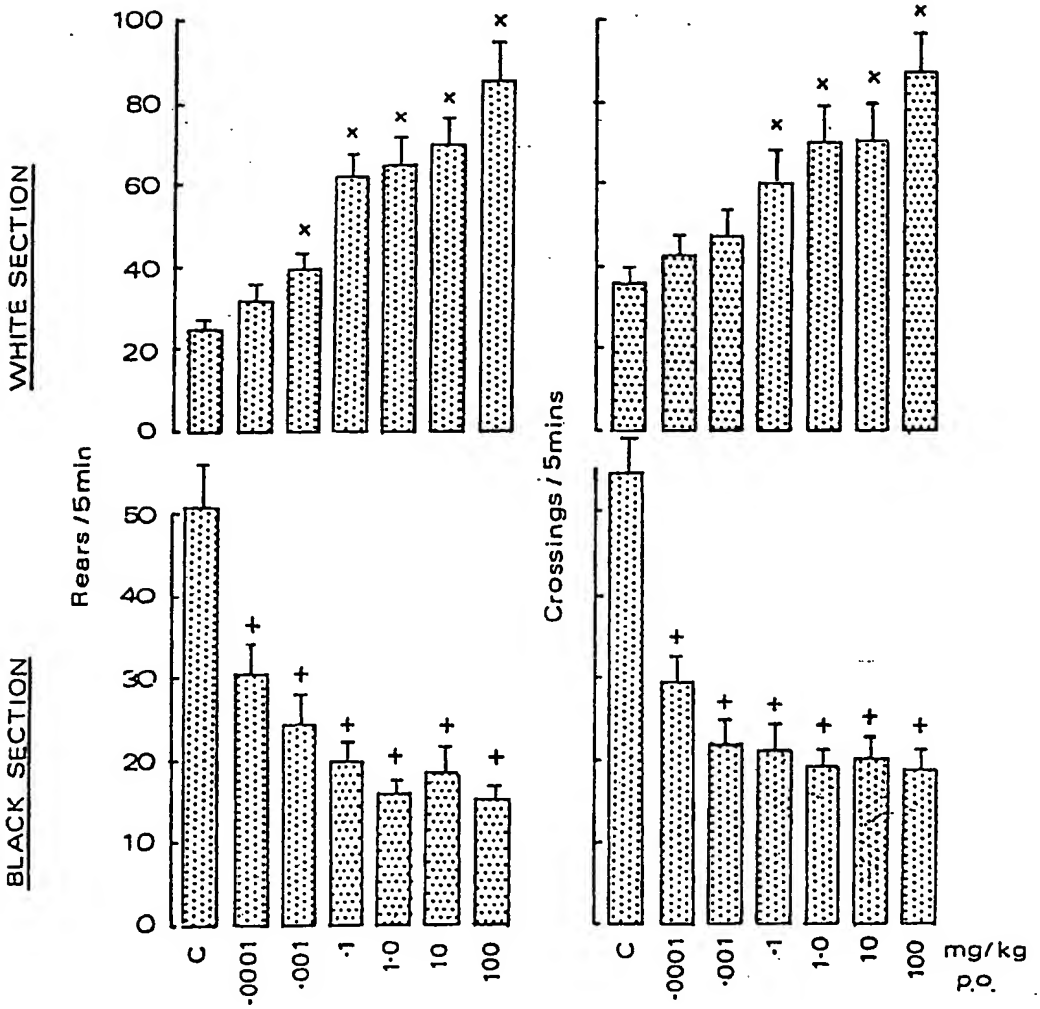

WHITE SECTION
BLACK SECTION
Rears / 5min
Crossings / 5mins
100
80
60
40
20
0
50
40
30
20
10
0
C
·0001
·001
·1
1·0
10
100
mg/kg
p.o.

FIG.8

FIG. 9

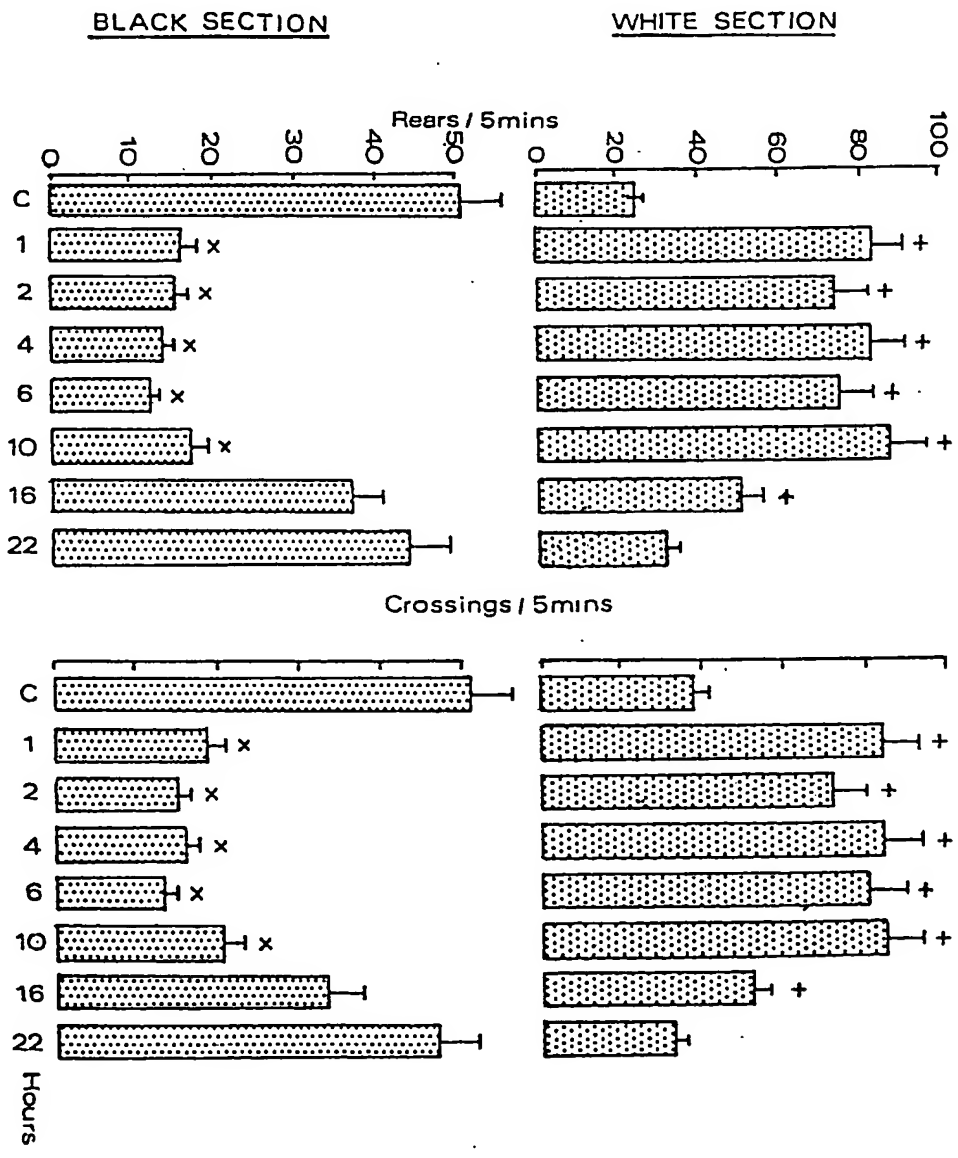
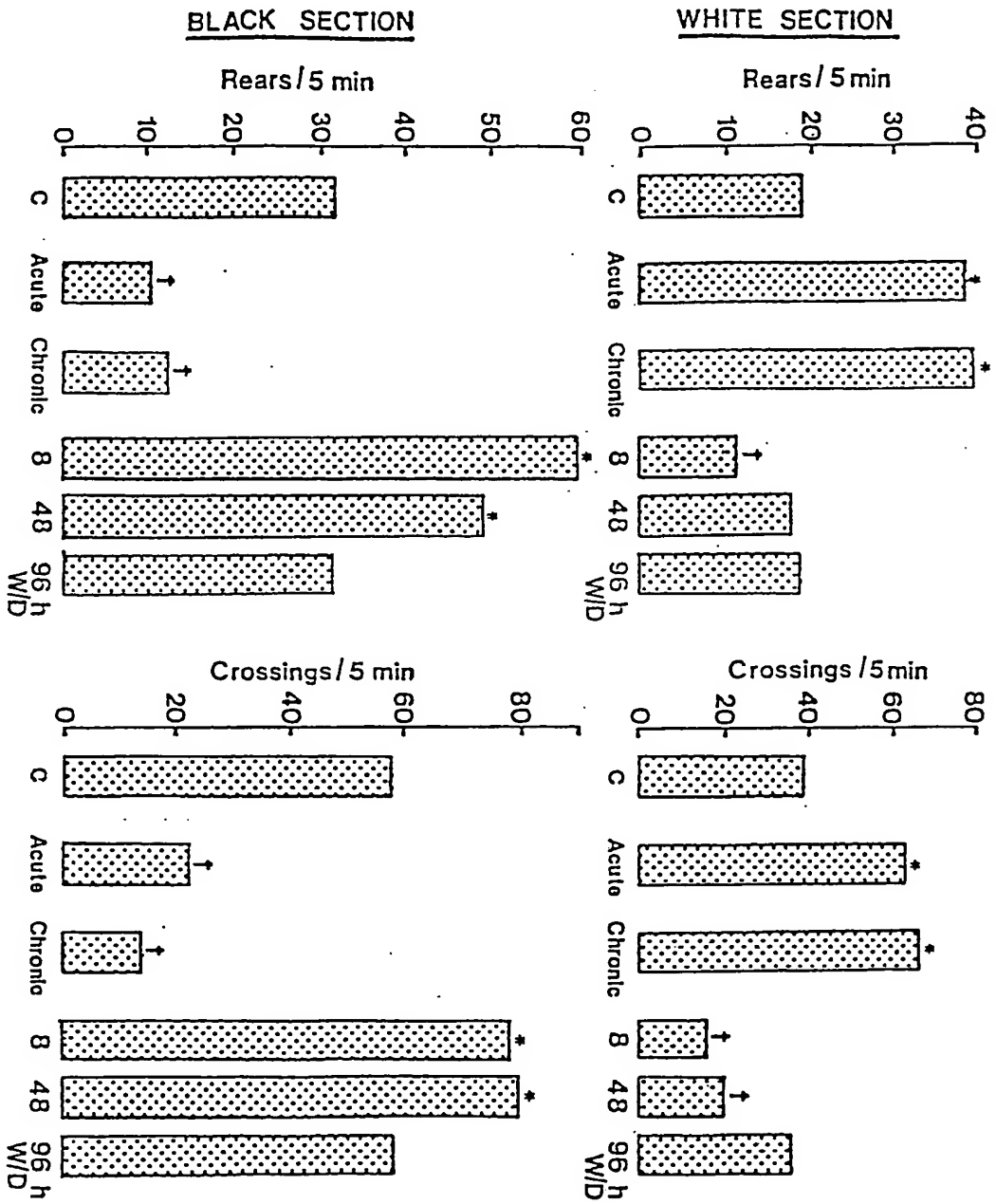

BLACK SECTION
WHITE SECTION
Rears / 5mins
0
10
20
30
40
50
0
20
40
60
80
100
C
1
2
4
6
10
16
22
×
+
Crossings / 5mins
Hours

FIG. 10


BLACK SECTION
WHITE SECTION
Rears / 5 min
Crossings / 5 min
0
10
20
30
40
50
60
80
C
Acute
Chronic
8
48
96 h W/D

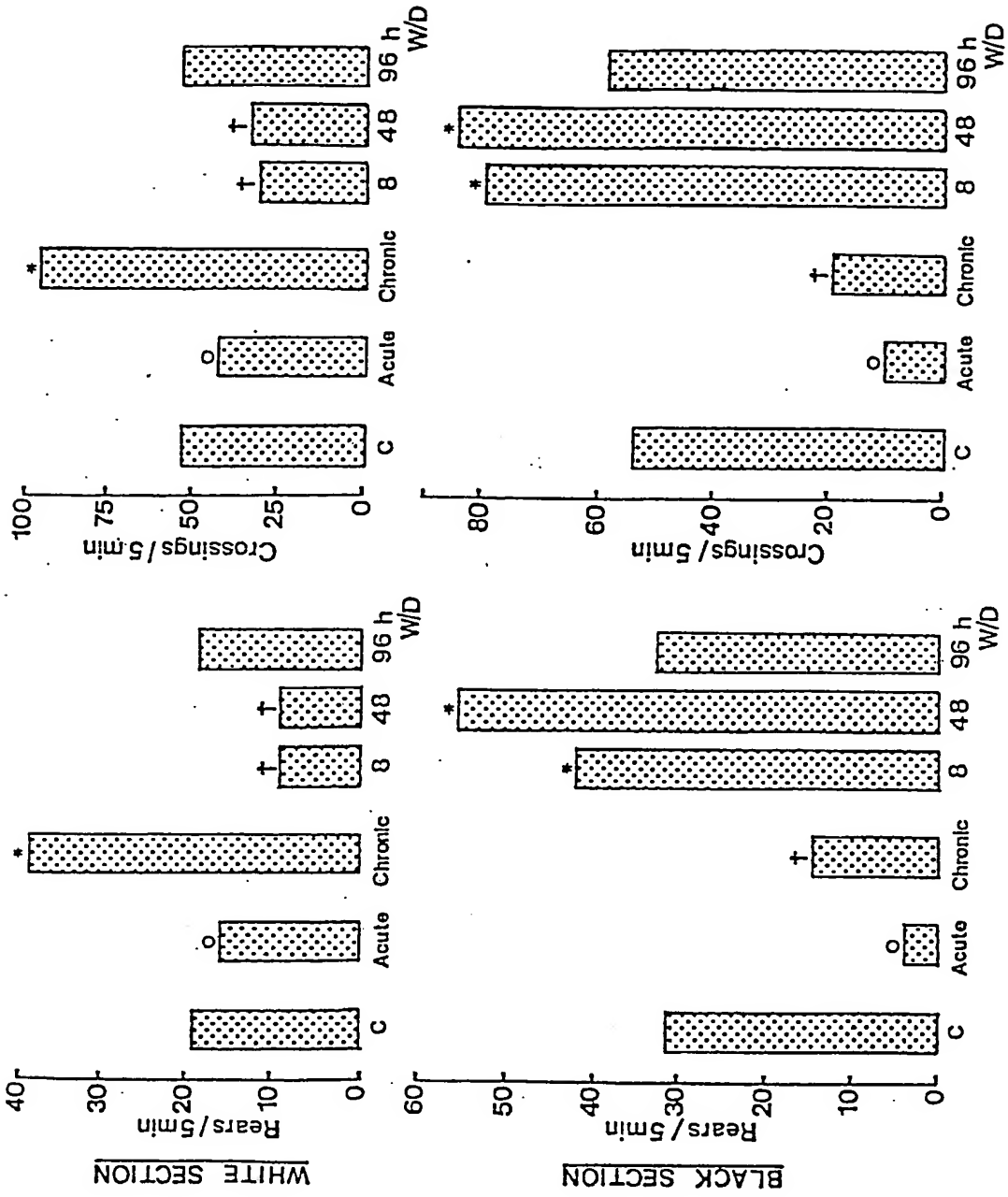

BLACK SECTION
WHITE SECTION
Crossings/5min
Crossings/5.min
Rears/5min
C
Acute
Chronic
8
48
96 h W/D

FIG.11

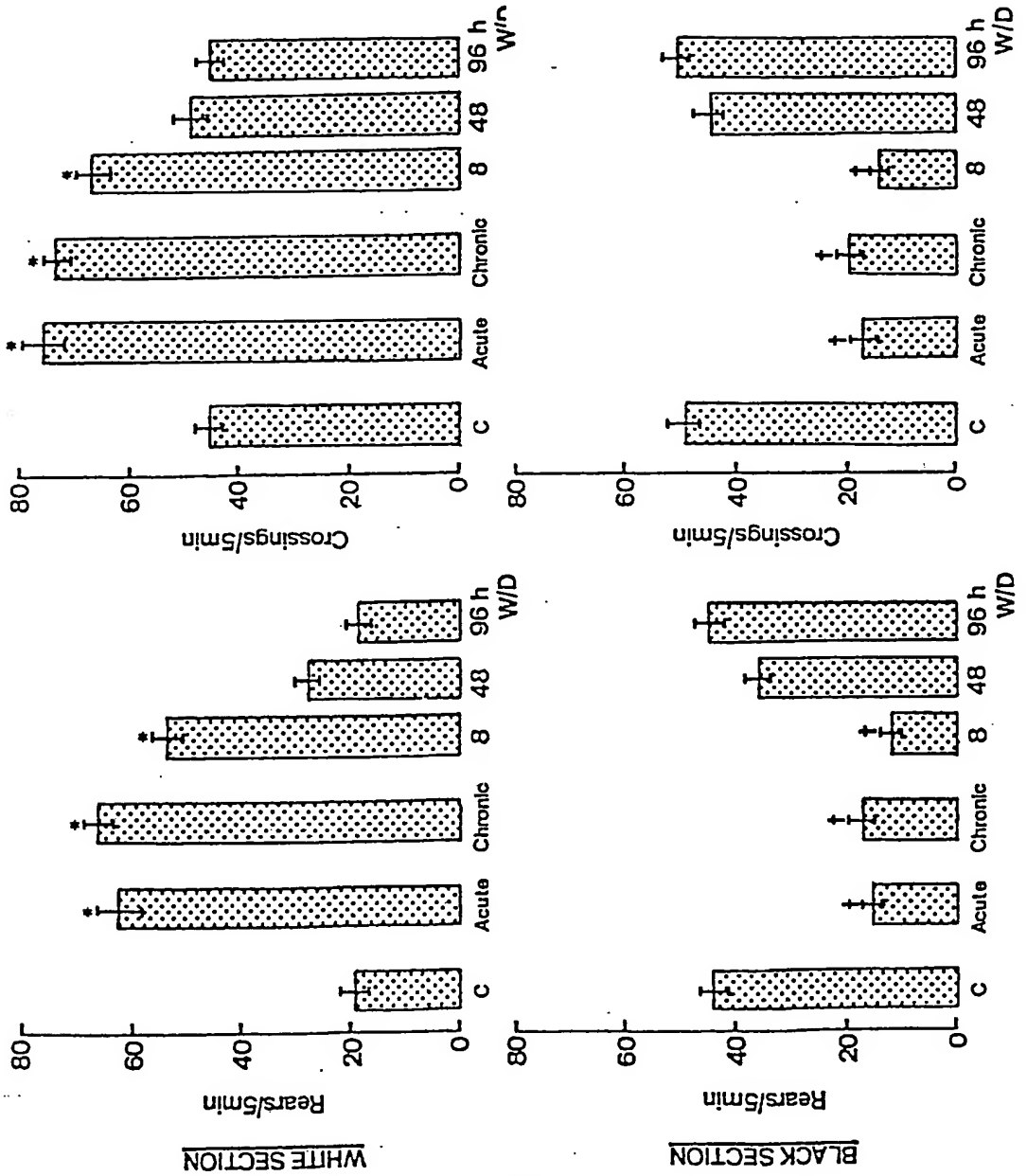

BLACK SECTION
WHITE SECTION
Crossings/5min
Rears/5min
0
20
40
60
80
C
Acute
Chronic
8
48
96 h
W/D

FIG.12

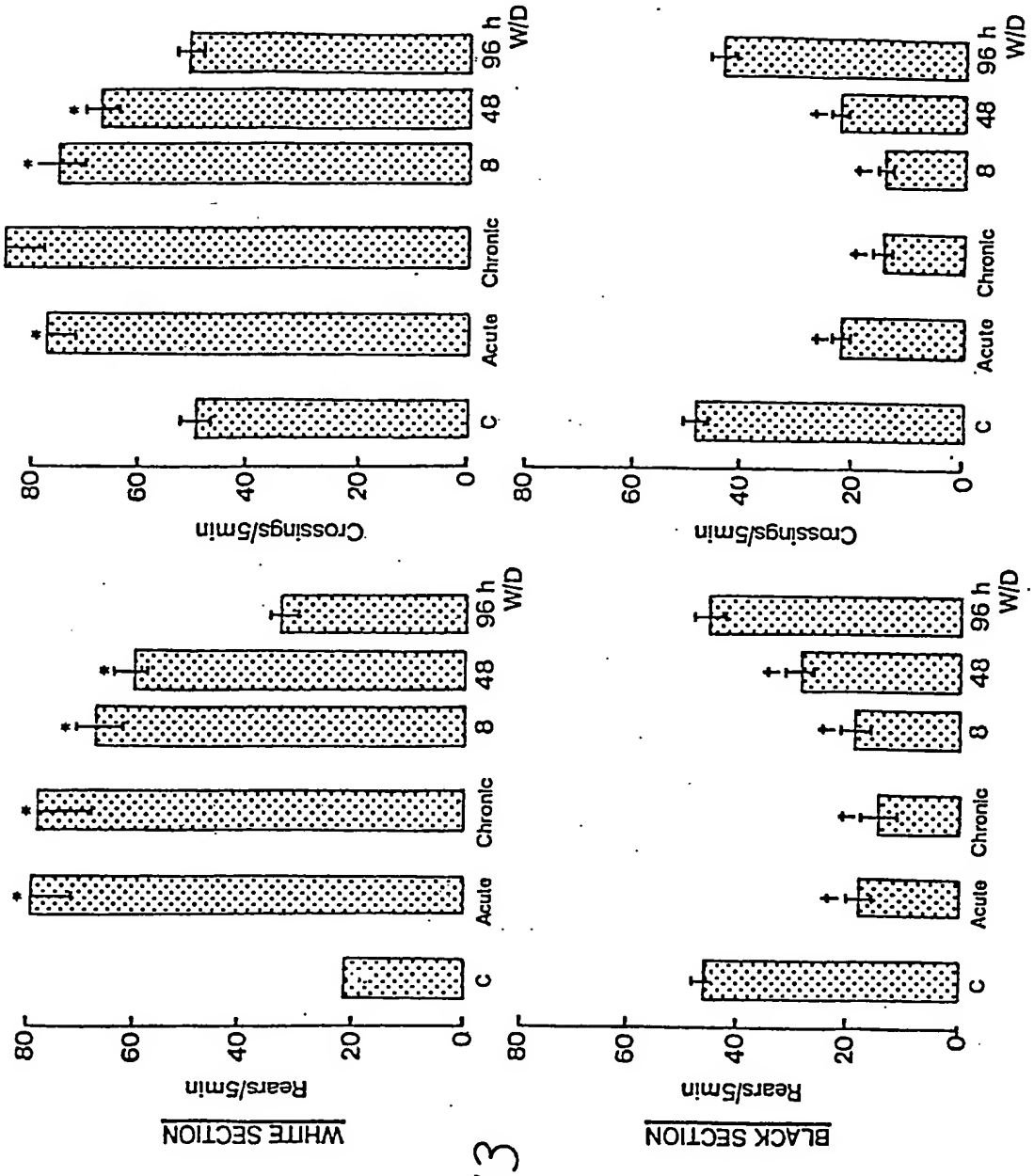

BLACK SECTION
WHITE SECTION
Rears/5min
Crossings/5min
0
20
40
60
80
C
Acute
Chronic
8
48
96 h
W/D

FIG. 13

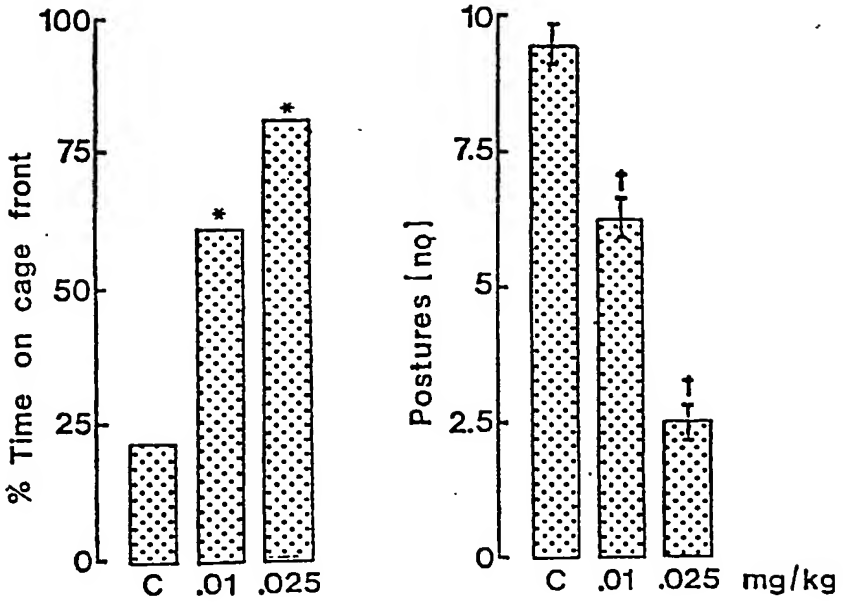

100
75
50
25
0
% Time on cage front
C
.01
.025
10
7.5
5
2.5
0
Postures [no]
C
.01
.025
mg/kg

FIG. 14

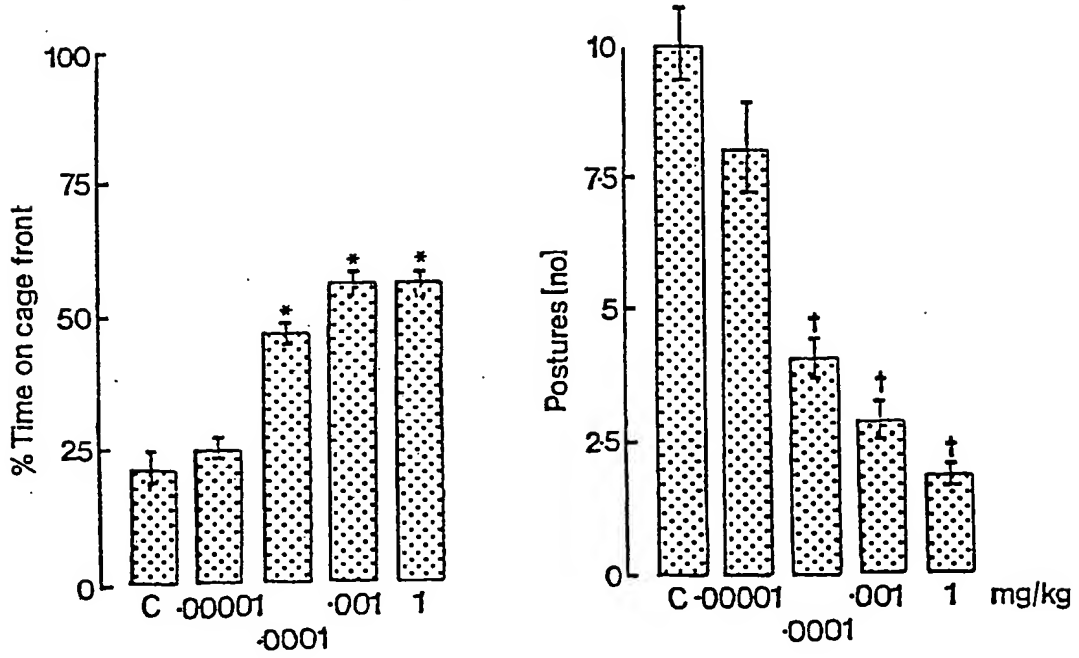

100
75
50
25
0
% Time on cage front
C
·00001
·0001
·001
1
10
7.5
5
2.5
0
Postures [no]
C
·00001
·0001
·001
1
mg/kg

FIG. 15

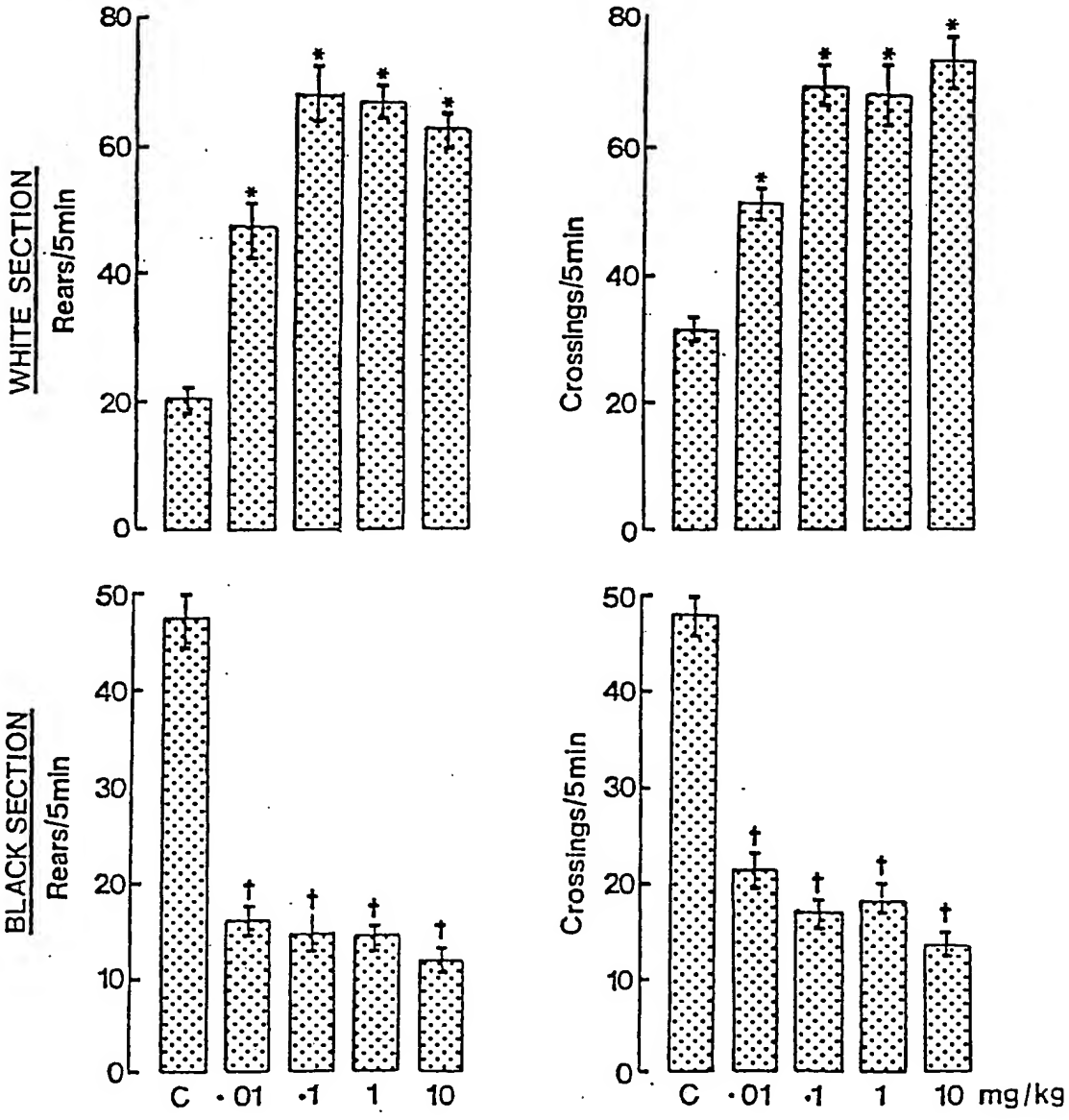

WHITE SECTION
Rears/5min
Crossings/5min
BLACK SECTION
Rears/5min
Crossings/5min
0
20
40
60
80
10
30
50
C
·01
·1
1
10
mg/kg

FIG. 16

SPECIFICATION

Anxiolytic compositions containing dioxopiperidine derivatives

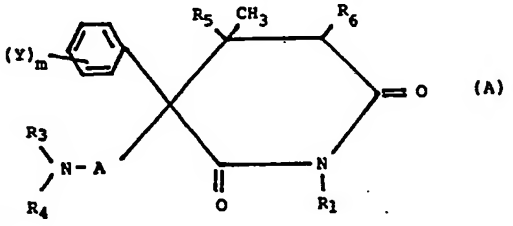
This invention relates to the use of certain 3-phenyl-3-aminoalkyl-4-methyl-2,6-dioxopiperidines as anxiolytic drugs. In particular, the invention provides the use of the said dioxopiperidines in the manufacture of anxiolytic medicaments, low dosage unit dose compositions comprising said dioxopiperidines, and methods of treatment of anxiety using said dioxopiperidines.

The most widely prescribed anti-anxiety drugs are benzodiazepines angonists such as diazepam and it is known that these drugs act by ineracting with a benzodiazepine receptor. When used in low doses they have virtually no side effects but their anti-anxiety effectiveness is often not sufficient. Increasing the dose to a normal effective one often produces side effects such as dizziness and sedation. These doses can also lead to memory impairment. Further, tolerance to their effect usually develops within four months of continuous use and there exists a substantial risk of addiction in many patients.

Benzodiazepine agonists are generally believed to exert their anxiolytic action by respectively enhancing the coupling function of the benzodiazepine receptor to the gamma-aminobutyric acid (GABA) receptor-chloride channel complex. It is also known that benzodiazepine agonists reduce the turnover of serotonin (5-hydroxytryptamine; 5HT) but the significance of this reduction has not previously been known.

It has surprisingly now been found that certain 3-phenyl-3-aminoalkyl-4-methyl-2,6-dioxopiperidines (as defined hereinafter) have strong anxiolytic activity.

GB 1455687 (also AU 480855, BE 808958, DE 2360526, FR 7346904, JP 6053014 and US 3963729) discloses that 3-phenyl-3-aminoalkyl-4- and/or 5-methyl-2,6-dioxopiperidine derivatives have central nervous system, especially antidepressant, activity. Said compounds include, *inter alia*, those of the following Formula A.



wherein:

R_1 represents hydrogen or C_1–C_4 alkyl;

R_3 represents hydrogen or C_1–C_4 alkyl;

R_4 represents C_1–C_4 alkyl;

R_5 and R_6 independently represent hydrogen or methyl;

A represents C_1–C_6 alkylene;

m is 0 to 3; and

Y is hydroxy, C_1–C_4 alkoxy, C_1–C_4 alkyl, C_1–C_4 hydroxyalkyl, halogen or trifluoromethyl.

The dose level specified for administration of the compounds is 0.1 to 100 mg/kg using pharmaceutical compositions containing 1 to 1000 mg per unit dose.

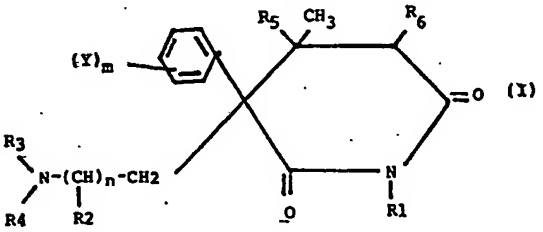
It also has been disclosed in U.S. 4,461,771 that compounds of Formula A, in which R_1 represents hydrogen; R_3 and R_4 independently represent methyl or ethyl; R_5 represents methyl; R_6 represents hydrogen; A represents ethylene or propylene; *m* is 1 or 2; and each Y is in a meta position and independently represents hydroxy or C_1–C_2 alkoxy, are belived to reduce *in vitro* the activity of tryptophan hydroxylase by blocking the depolarization-induced activation of the enzyme in the brain stem and hence are of potential use in the prophylactic treatment of the stressful disorder migraine. The dose level specified for this treatment is 0.01 to 10 mg/kg, especially 0.1 to 3 mg/kg, using pharmaceutical compositions containing 0.1 to 200 mg, usually 1 to 100 mg, per unit dose. More recently, it has been reported that at least one compound of Formula A (viz 3-(3'-methoxy-phenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine; AGN 2979) also blocks *in vitro* the activation of tryptophan hydroxylase resulting from exposure of brain stem slices to metabolic inhibitors or methylxanthines or induced by incubation of supernatant preparations of the enzyme under phosphorylating conditions (Boadle-Biber, M.C. *et al* Biochem. Pharmacol. *35*, 1521-6, (1986)). However, it also has been reported that AGN 2979 has no significant effect *in vitro* upon the unactivated enzyme (Boadle-Biber, M.C. *et al* supra).

Further, it has recently been disclosed in GB 2181346A that compounds of Formula A, in which R_1 represents hydrogen; R_3 and R_4 independently represent methyl or ethyl; A represents ethylene or propylene; *m* is 1 or 2; and each Y is in a meta position and independently

represents hydroxy or C_1–C_2 alkoxy, are believed to reduce the turnover of 5-hydroxytryptamine (5HT) resulting from inhibiting the activity of tryptophan hydroxylase. They are reported to have anxiolytic activity, antagonize the anxiogenic activity of benzodiazepines inverse agonists, reduce chronic abnormally high brain levels of 5HT or its metabolite 5-hydroxy-indoleacetic acid, and have antibacterial and antiviral activity.

G.B. 2181346A was published in pursuance of U.K. Patent Application No. 8621577 filed 8th September 1986 and claiming priority from U.K. Patent Applications Nos. 8522455 (filed 11th September 1985), 8603909 (filed 17th February 1986) and 8603910 (also filed 17th February 1986). Originally, it was thought that the disclosed compounds were not themselves anxiolytic because they have virtually no action at benzodiazepine receptors and that they acted via some unknown pharmacological mechanism to potentiate the anxiolytic activity of benzodiazepine receptors. Their anxiolytic activity was disclosed for the first time in U.K. Patent Application No. 8621577. At that time, the compounds were believed to be active in the range 0.1 to 20 mg/kg, especially 0.5 to 10 mg/kg and hence pharmaceutical compositions containing 10 to 500 mg, especially 10 to 100 mg, were proposed. However, it has now surprisingly been found that the compounds are active at much lower dose levels, down to nanogram/kg amounts.

According to a first aspect of the present invention, there is provided the use in the manufacture of a medicament for the treatment of anxiety of a compound of the following Formula I.



wherein:

R_1 represents hydrogen or C_1–C_4 alkyl;

n is 1 or 2;

R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;

n is 1 or 2;

R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;

R_3 represents hydrogen or C1–C2 alkyl;

R_4 represents C1–C2 alkyl;

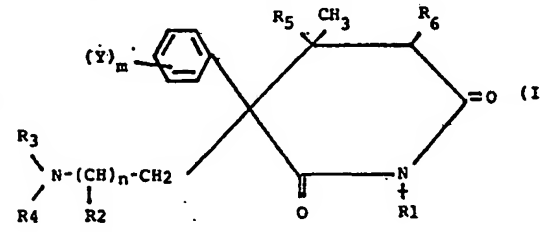
R5 and R6 independently represent hydrogen or methyl;

m is 0 to 3; and

each Y is in a meta or para position and independently represents hydroxy, C_1–C_2 alkoxy, C_1–C_2 alkyl, C1–C2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,

or a pharmacologically acceptable salt thereof.

In a second aspect, the invention provides a method of treating a patient suffering from anxiety, which comprises administering to the patient an anti-anxiety effective amount of a compound of the following Formula I.



wherein:

R_1 represents hydrogen or C_1–C_4 alkyl;

n is 1 or 2;

R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;

R_3 represents hydrogen or C_1–C_2 alkyl;

R_4 represents C_1–C_2 alkyl;

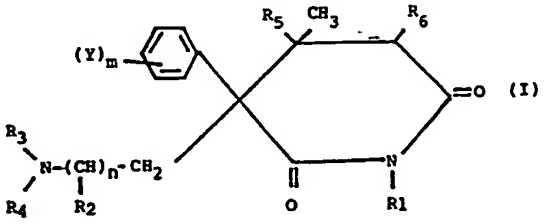
R_5 and R_6 independently represent hydrogen or methyl;

m is 0 to 3; and

each Y is in a meta or para position and independently represents hydroxy, C_1–C_2 alkoxy, C1–C2 alkyl, C1–C2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy

are not in the para position,
or a pharmacologically acceptable salt thereof.

According to a third aspect of the invention, there is provided a pharmaceutical composition in unit dose form comprising, with a pharmaceutically acceptable diluent or carrier an amount of 10^{-7} to 10^{-1} mg per unit dose of a compound of the following Formula I:



wherein:
R_1 represents hydrogen or C_1–C_4 alkyl;
n is 1 or 2;
R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;
R_3 represents hydrogen or C1–C2 alkyl;
R_4 represents C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl;
m is 0 to 3; and
each Y is in a meta or para position and independently represents hydroxy, C_1–C_2 alkoxy, C_1–C_2 alkyl, C_1–C_2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,
or a pharmacologically acceptable salt thereof.

The compounds of Formula I can be prepared in the manner disclosed in GB 1455687. They exist as optical isomers and can be used in racemate form or as individual (+) or (−) isomers. Presently, the (−) isomer is preferred.

As mentioned above the compounds of Formula I have anxiolytic activity and hence are useful in the treatment of anxiety. At least some of the compounds are ten orders (10^5) more potent than diazepam and exhibit an effective dose range in the order of millions fold (eg. 10^{-4}–10^2 mg/kg). They cause dose related anxiolytic effects and do not cause sedation at high doses (10^2 mg/kg).

The compounds of Formula I can be administered in various manners to achieve the desired anxiolytic effect. The compounds can be administered enterally or parenterally to the patient being treated. Oral administration is likely to be the preferred route in most circumstances but injection, especially subcutaneously or intravenously, will be preferred in some circumstances.

The amount of compound administered will vary and can be any anti-anxiety effective amount. Depending upon the patient and the mode of administration, the amount of compound administered may vary over a wide range to provide from about 10^{-7} to 10^2 mg/kg, usually 10^{-5} to 10^2 mg/kg, especially 10^{-4} to 10^2 mg/kg, of body weight of the patient per unit dose. Unit doses of these compounds can contain, for example, from about 10^{-6} mg to 500 mg, usually 10^{-4} to 102 mg, especially 10^{-3} to 102 mg of the compound and may be administered, for example, from 1 to 4 times daily.

The term "unit dosage form" is used herein to mean a single or multiple dose form containing a quantity of the active ingredient in admixture with or otherwise in association with a diluent or carrier, said quantity being such that one or more predetermined units are normally required for a single therapeutic administration. In the case of multiple dose forms such as liquids or scored tablets, said predetermined unit will be one fraction, such as a 5 ml (teaspoon) quantity of a liquid or a half or quarter of a scored tablet, of the multiple dose form.

The compounds of Formula I have virtually no action at benzodiazepine receptors. The capacity of a selected number of compounds of Formula I to displace triturated flunitrazepam from benzodiazepine receptors has been measured with the results set forth in Table I below:-

TABLE 1

	COMPOUND OF FORMULA I				
	2979	3222	2939	3181	DIAZEPAM*
IC50(uM) [^{3}H] Flunitrazepam Binding	350	1300	9000	6700	0.014

* 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one

The compounds of general Formula I can have the phenyl moiety substituted in one or both meta positions by C_1–C_2 alkyl, C_1–C_2 hydroxyalkyl, halogen, trifluoromethyl, or, preferably, hydroxy or C_1–C_2 alkoxy. Additionally or alternatively, the phenyl moiety can be substituted in the para position by the aforementioned groups other than hydroxy and alkoxy. It is presently preferred that the substituents(s) should be hydroxy or, especially, methoxy. It is also preferred that one or both meta positions are substituted and that, when there are two substituents, they should be the same.

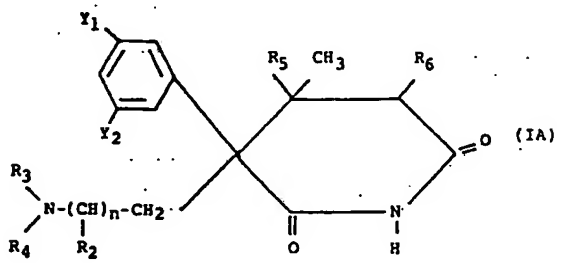
The amino group of the compounds of Formula I can be secondary or tertiary having methyl or ethyl groups attached to the nitrogen atom. Dimethylamino presently is preferred. The amino group is connected to the piperidine ring by a divalent ethylene (i.e. n=1) or trimethylene (i.e. n=2) radical optionally substituted on a carbon atom not adjacent said ring with a methyl group. Presently, unsubstituted trimethylene is preferred.

The piperidine ring of the compounds of Formula I is substituted in the 4-position with methyl and optionally by one or two further methyl groups in the 4 and/or 5 positions. It is presently preferred that there is one further methyl group in the 4 or 5 position, especially in the 4-position.

The ring nitrogen atom of the piperidine ring can be substituted with a C_1–C_4 alkyl group but it is presently preferred that said nitrogen atom is unsubstituted.

The C_1–C_2 alkyl groups or moieties referred to herein are methyl or ethyl; methyl presently being preferred. The C_3–C_4 alkyl groups which may be substituents on the nitrogen atom of the piperidine ring can be straight or branched chain but the straight chain n-propyl or n-butyl groups presently are preferred. The halogen substituents(s) in the phenyl ring can be chlorine, bromine or fluorine; chlorine presently being preferred.

The presently preferred compounds of Formula I are those of the following Formula IA.



wherein:

n is 1 or 2;

R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;

R_3 represents hydrogen or C_1–C_2 alkyl;

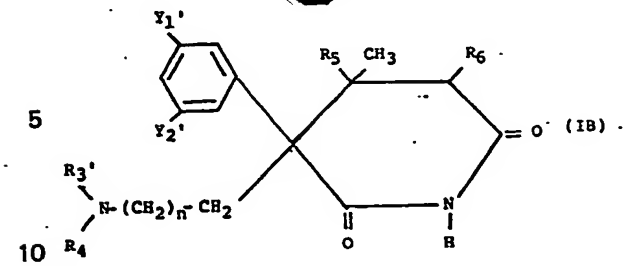
R_4 represents C_1–C_2 alkyl;

R_5 and R_6 independently represent hydrogen or methyl; and

Y_1 and Y_2 independently represent hydrogen, hydroxy or C_1–C_2 alkoxy,

or a pharmacologically acceptable salt thereof.

The presently especially preferred compounds of Formula 1A are those of the following Formula IB.



wherein:
n is 1 or 2;
R_3' and R_4 independently represent C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl;
Y_1' represents hydroxy or C_1–C_2 alkoxy; and
Y_2' represents hydrogen, hydroxy or C_1–C_2 alkoxy,
or a pharmacologically acceptable salt thereof.

Examples of compounds of Formula IC include the following:-3-(3'-methoxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine
3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine (AGN 2979);
3-(3'-methoxyphenyl)-3-(2"-N,N-diethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3'-methoxyphenyl)-3-(3"-N,N-diethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3'-hydroxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3'-hydroxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3'-methoxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,5-dimethyl-2,6-dioxopiperidine (AGN 2939);
3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,5-dimethyl-2,6-dioxopiperidine (AGN 3181);
3-(3'-ethoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3'-ethoxyphenyl)-3-(3"-N,N-diethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3', 5'-dimethoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine (AGN 3222);
3-(3',5'-dimethoxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(3',5'-dimethoxy phenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine; and
3-(3',5'-dimethoxyphenyl)-3-(2"-N,N-dimethylamioethyl)-4,5-dimethyl-2,6-dioxopiperidine;

Examples of other compounds of Formula I include:-
3-phenyl-3-(2'-N,N-dimethylaminoethyl)-4-methyl-2,6-dioxopiperidine;
3-phenyl-3-(2'-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-phenyl-3-(2'-N,N-dimethylaminoethyl)-4,5-dimethyl-2,6-dioxopiperidine;
3-phenyl-3(3'-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;
3-(4'-chlorophenyl)-3(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine; and
3-phenyl-3(2' N-methylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine.

The compounds of Formula I may be administered in free base form, as an alkali metal or alkaline earth metal salt or as a pharmaceutically acceptable acid addition salt with the proviso that an alkali metal or alkaline earth metal salt is not normally combined with an acid addition salt except in a layer formulation.

Representative acid addition salt forms include organic acid salt forms such as the maleate and methane sulphonate and mineral acid salt forms such as hydrochloride and perchlorate.

The pharmaceutical formulations in which form the active compounds of the invention will normally be utilized are prepared in a manner well known in the pharmaceutical art and usually comprise at least one active compound of Formula I admixture or otherwise in association with a pharmaceutically acceptable carrier therefor. For making those formulations the active ingredient will usually be mixed with a carrier, or diluted by a diluent, or enclosed or encapsulated in a capsule, sachet, cachet, or other container. A carrier or diluent may be solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active ingredient. Suitable carriers or diluents are well known *per se*.

The formulations may be adapted for enteral or parenteral and may be administered to the patient in the form of tablets, capsules, dragees, suppositories, syrups, suspensions or the like.

The formulations may be in delayed or sustained release form.

Aside from the active agents the compositions may contain pharmaceutically inert organic or inorganic adjuvants, optionally granulating agents, binding agents, lubricants, dispersing agents, wetting agents and preservatives. Moreover, the pharmaceutical compositions may contain col-

ouring, flavouring and sweetening substances. Adjuvants for the production of tablets may be e.g. calcium carbonate, lactose micro-crystalline cellulose, mannitol or talc. Starch and alginic acid or micro-crystalline cellulose may be used as granulating and disintegrating agents, starch, polyvinylpyrrolidone and gelatine may be used as binding agents and magnesium stearate, stearic acid, colloidal silica and talc as lubricants. Tablet formulation may be coated or uncoated, the coating having the purpose of delaying the disintegration and absorption in the gastrointestinal tract. Suitable suspending agents for the production of liquid administration forms are e.g. methyl cellulose and sodium alginate. Capsule formulation may contain the active agents on their own or together with an inert solid diluent e.g. calcium phosphate, corn starch, lactose, or mannitol.

The invention is illustrated in the following non-limiting Examples.

EXAMPLE 1

Tablet Formulation

Tablets each having the following composition are prepared by conventional techniques:

	mg/tablet
(a) Compound AGN 2979 base	1
(b) Lactose	51.5
(c) Maize starch dried	45
(d) Magnesium stearate	1.5

EXAMPLE 2

Suppository Formulation

	mg/suppository
(a) Compound AGN 2979 HCl	10
(b) Oil of Theobroma (cocoa butter)	990

The compound (a) is powdered and passed through a BS No. 100 sieve and triturated with molten oil of Theobroma at 45°C to form a smooth suspension. The mixture is well stirred and poured into moulds each of nominal 1 G capacity to produce suppositories.

EXAMPLE 3

Tablet Formulation

(a) Compound AGN 2979 base	10mg
(b) Wheat starch	7g
(c) Lactose	20g
(d) Magnesium Stearate	1g

The mixture is compressed into 1000 tablets each weighing 138 mg.

EXAMPLE 4

Pill Formulation

	per pill
(a) Compound AGN 2979 HCl	10mg
(b) Corn starch	45mg
(c) Liquid glucose	7ml

The pills are prepared by blending the active ingredient (a) and the corn starch, then adding the liquid glucose with thorough kneading to form a plastic mass from which the pills are cut and formed.

EXAMPLE 5

Gelatine Capsule Formulation

	per capsule
(a) Compound AGN 2979 HCl	2.5mg
(b) Talc	70mg

A capsule is prepared by passing dry powdered active ingredient (a) and powdered talc in the above proportions through a fine mesh screen and mixing them well. The powder is then filled into hard gelatin capsules at a net fill of 72.5mg per capsule.

EXAMPLE 6

Experimental animals

Naive male albino BKW mice, 25–30g, were used in all experiments. 10 were normally housed in each cage and given free access to food and water. The mice were kept on a 12h light and 12h dark cycle with lights off at 8.00 am and on at 8.00 pm.

Anti-anxiety test

The apparatus used for the detection of changes in anxiety consisted of an open topped box (81×36×27cm high) one third painted black and illuminated under a dim red light (1×60W) and partitioned from the remainder of the box which was painted white and brightly illuminated with a 100W light source located 17cm above the box. Access between these areas was enabled by means of a 7.5×7.5. cm opening located at floor level in the centre of the partition. The floor area was marked by lines into 9cm squares. The test was conducted between 13.00h and 18.00h in a quite, darkened room illuminated with red light only. Animals were thus taken in a dark container from a dark holding room to the dark testing room.

Animals that had received rug or vehicle injections were placed individually into the centre of the white area and their behaviour observed over a 5 minute period by remote video recording. Four behavioural parameters were noted every minute; viz the number of exploratory rearings in the white and black sections, the number of line crossings in the white and black areas, the number of transitions between the white and black or black and white areas, and the time spent in the white and black areas. Experimenters remained blind to drug treatment throughout, with the code only being broken after analysis was complete.

Experimental design

Animals were used in treatment groups of 5 and vehicle controls were run on each day of testing. Results were analysed using Single-Factor Analysis of Variance and, where appropriate, followed by Dunnett's procedure for comparing all treatments with control.

Drugs

(±) AGN 2979 was prepared in distilled water and diazepam (Roche) in the minimum quantity of polyethylene glycol (less than 25%) was prepared to volume with distilled water. Doses (expressed as the base) were administered as a 60 min pretreatment in a volume of 1ml/100g body weight by intraperiotoneal (diazepam) or subcutaneous (AGN 2979) injection.

The results are indicated in accompanying Figs. 1, 2 and 3 and discussed below.

Fig. 1 shows the changes in rearing behaviour and line crossings (locomotion) in the white and black sections of the box for diazepam given intraperitoneally. C indicates the responses of vehicle-treated, control animals. n=5, except for C where n=15. S.E.M.s less than 11.6%. Significant increases in responding are indicated as *P less than 0.001, significant decreases as +P less than 0.05-P less than 0.001 (one-way ANOVA followed by Dunnett's 't' test).

Fig. 2 shows the changes in rearing behaviour and line crossings (locomotion) in the white and black sections of the box for AGN 2979 given subcutaneously into the back neck region. C indicates the responses of vehicle-treated, control animals. n=5, except for C where n=15. S.E.M.s less than 7.3%. Significant increases in responding are indicated as +P less than 0.001, significant decreases as*P less than 0.01-P less than 0.001 (one-way ANOVA followed by Dunnett's 't' test).

Fig 3 shows the changes in the time spent by mice in exploration of the black section of the box for AGN 2979 injected subentaneously into the back neck region. C indicates the response of vehicle-treated control animals. n=5, except for C where n=15. S.E.M.s on original data less than 6.6%. Significant decreases in the time spent in the black sections are indicated as *P less than 0.01—less than 0.001 (one-way ANOVA followed by Dunnett's 't' test). *General observations*

Within the test situation vehicle-treated animals displayed a characteristic behavioural profile which is typified as follows:

(1) an approximately equal time spent in each section of the test area;

(2) a transition rate between the two areas in the order of 8.3±0.1/5 min;

(3) a significant difference between locomotion in the white section (33.7±3.0/5 min) and line crossing in the black (53.5±4.9/5 min)

(4) a marked increase in rearing in the black section (49.7±3.2/5 min) as compared to the incidence of this behaviour in the white (22.1±1.5/5 min).

These data indicate that, under test conditions, animals display a marked preference for activity in the black section of the test area, possibly induced by the aversive properties of the brightly-lit white painted area. Intuitively these findings may have been expected in view of the nocturnal nature of the species employed. Preference for the black section is most clearly demonstrated by measures of locomotion and rearing.

Detailed initial studies showed that the responses of vehicle treated animals were not significantly different (P greater than 0.05) from those derived above for non-treated control animals. Hence, only the responses obtained from vehicle-treated animals are given as control data.

Modification of exploratory behaviour by diazepam

Diazepam (0.125-5.0mg/kg) caused a 2 to 4 fold increase in rearing and 1.5-2 fold increase in line crossings in the white area. A lower dose of 0.063mg/kg was ineffective, emphasising the all or none nature of the response. A higher dose of 10mg/kg caused sedation and a reduction of rearings and line crossings. The increased rearings and line crossings in the white area was mirrored by a reduction in these behaviours in the black area (Fig. 1).

Modification of exploratory behaviour by AGN 2979

AGN 2979 was as effective as diazepam to enhance rearings and line crossings in the white area and, as seen with diazepam, such changes correlated with reduced rearings and line crossings in the dark area (Fig.2). The most notable features of the action of AGN 2979 were (a) its exceptional potency (0.00001–100.0 mg/kg) to increase behavioural measures in the white section, (b) the exceptional dose range at which the responses could be obtained (doses were administered over a range to the order of 10 million (10^6), and (c) the dose related effects of AGN 2979 which contrasts with the all-or-none response of diazepam. Additionally mice treated with AGN 2979 showed a marked reduction in time spent in the black section (Fig. 3) and, importantly, the effects of AGN 2979 were achieved in the absence of sedation.

Example 7

The procedure of Example 6 was repeated except that separate groups of mice were tested 0.5, 1, 2, 4 and 6h after subcutaneous administration of 0.1 mg/kg or 10 mg/kg (±) AGN 2979 in distilled water. The results were analysed using Single-Factor Analysis of Variance by Dunnetts procedure for comparing all treatments with vehicle-treated mice as control. They are indicated in accompanying Figs. 4 and 5 and discussed below.

Fig. 4 shows the changes in rearing behaviour and line crossings (locomotion) in the black and white sections of the box for 0.1 mg/kg AGN 2979 given subentaneously into the back neck region. C indicates that responses of vehicle-treated control animals. n=5. S.E.M.s given. Significant increases in responding are indicated as *P less than 0.05, **P less than 0.01-P less than 0.001, significant decreases as ++P less than 0.01-P less than 0.001 (one-way ANOVA followed by Dunnett's "t" test).

Fig. 5 corresponds to Fig. 4 for the subcutaneous injection of 10 mg/kg AGN 2979 into the back neck region.

The anxiolytic action of AGN 2979, characterised by increased rearing and locomotion in the white section of the test box to which mice are normally averse, with corresponding decreases in behaviour in the black compartment, was seen to develop within 30 minutes of administering 0.1 mg/kg AGN 2979, although the maximum effect was not attained for 1h. The anxiolytic action was then maintained for the following administration, with return to control values after 6h (Fig. 4). A similar course of onset and duration was recorded for 10 mg/kg AGN 2979 but, using this dose, the anxiolytic action was more established after 30 minutes than at the lower dose, and the maximum effect was well sustained over a 4h period. However, as observed at the lower dose, the anxiolytic acitivity was no longer detectable after 6h.

EXAMPLE 8

Male Sprague-Dawley rats, 225-275g, were normally housed in groups of 5 and kept on a 12h light/dark cycle with lights on at 08.00 h. Tests were conducted between 13.00 and 18.00 h in a brightly illuminated room.

The apparatus used for the detection of changes in social interaction consisted of an opaque white Perspex (TM) open-topped box (45×32cm×20cm high) with 15×16 cm areas marked on the floor. Two native rats, taken from separate housing cages were placed in the test box (with a 100W bright white illumination 17 cm above) and their behaviour observed over a 10 minute period by remote video recording. Social interaction between animals was determined by timing (seconds) sniffing of partner, crawling under or climbing over partner, grooming partner, genital investigation of partner, following partner. In addition, exploratory locomotion was measured as the number of crossings of the lines marked on the box floor.

The experimental design was to use rats in groups of 6 (i.e. 3 pairs). (±) AGN 2979 was prepared in distilled water and diazepam (Roche) in the minimum quantity of polyethylene glycol (25%) prepared to volume with distilled water. Doses are expressed as the base and were administered by the intraperitoneal route as a 40 min pretreatment in a volume of 1 ml/kg body weight.

The results are indicated in accompanying Figs. 6 and 7 and discussed below.

Fig. 6 shows the effects of diazepam on rat social interaction (seconds in 10 minutes) and exploratory locomotion (number of line crossings 10 minutes) of pairs of weight matched rats placed in an observation box. n=6. S.E.M.s are given. Significant increase in social interaction is indicated as *P less than 0.001 (one-way ANOVA followed by Dunnett's t ... ° indicates sedation.

Fig. 7 shows the effects of AGN 2979 on rat social interaction (seconds [illegible]0 minutes) and exploratory locomotion (number of line crossings/10 min) of paired rats placed in an observation box. n=6. S.E.M.s are given. Significant increase in social interaction is indicated as *P less than 0.01–P less than 0.001 (one-way ANOVA followed by Dunnett's t test).

EXAMPLE 9

The procedure of Example 6 was repeated except for the following differences:-

a) *Dose-ranging experiment*

Mice were given the following oral doses of (±) AGN 2979;
0.0001, 0.001, 0.1, 1.0, 10.0, 100.0mg/kg p.o.
Tests were carried out 90 minutes after dosing.

b) *Duration of action experiment*

Thirty-five mice were given 100mg/kg (±) AGN 2979 p.o. and groups of 5 mice were studied at the following times after dosing:
1,2,4,6,10,16,22 hours
Three vehicle control groups were studied at intervals throughout the time of the experiment.
AGN 2979 was prepared in distilled water. Doses are expressed as the base and were administered by gavage in a volume of 2ml/100g body weight.

The results are indicated in accompanying Figs. 8 and [illegible] and discussed below.

Fig. 8 shows the changes in rearing behaviour and line crossings (locomotion) in the white and black sections of the box. C indicates the responses of [illegible]hicle-treated control animals. n=5 for each group. Significant increases in responding are indic[illegible]d as +p less than 0.01–p less than 0.001 (one-way ANOVA followed by Dunnett's 't' test).

Fig. 9 shows the changes in rearing behaviour and line crossings (locomotion) in the white and black sections of the box. C indicates the responses of [illegible]hicle-treated control animals. n=5 for each group. Significant increases in responding are indic[illegible]d as +p less than 0.001; significant decreases as ×p less than 0.01–p less than 0.001 (o[illegible]y ANOVA followed by Dunnett's 't' test).

General Observations

Within the present test situation vehicle-treated anim[illegible]isplayed a characteristic behavioural profile which is typified as follows:
(1) an approximately equal time spent in each section [illegible] the test area;
(2) a transition rate between the two area in the ord[illegible] 8.3±=.1/5 min;
(3) a significant difference between locomotion in th[illegible]e section 38.4±3.8/5 min) and line corssing in the black 51.2±5.3/5 min);
(4) a marked increase in rearing in the black section [illegible]±5.2/5 min) as compared to the incidence of this behaviour in the white 24.6±2.7/5 m[illegible]

The anxiolytic action of AGN 2979, characterised by [illegible]ased rearing and locomotion in the white section of the test box to which mice are norma[illegible]rse, with corresponding decreases in behaviour in the black compartment, was seen at th[illegible]vest dose used (0.0001 mg/kg p.o.). The effect was found to be dose-related with a near-m[illegible]al effect seen at 1.0-10.0 mg/kg p.o. After a dose of 100mg/kg p.o., the anxiolytic act[illegible]was shown to develop within 1 hour of administration. The effect was maximal 1 hour pos[illegible]and was maintained at this level for at least 10 hours. The anxiolytic effect, while still [illegible]tant, was beginning to decline at 16 hours and there was a return to control values 22 ho[illegible]r dosing.

EXAMPLE 10

The procedure of Example 6 was repeated to deter[illegible]e effects of abrupt withdrawal from long term treatment with diazepam (2.5 and 10 mg/k[illegible]) AGN 2979 (0.1 and 10 mg/kg). The experimental protocols were as follows:

1. Diazepam 10 mg/kg was given i.p. acutely or tw[illegible]y f[illegible] 7 days. This dose of diazepam is the lowest to cause sedative problems o[illegible] tre[illegible]ent; but tolerance to this rapidly develops on long-term treatment and, therefo[illegible]lo[illegible]as selected as the highest which could be given long-term for maintenance of a [illegible]ic action without complicating problems of sedation. The effects of acute treatment [illegible]cluded in the studies only for the purpose of comparison of anxiolytic response to short [illegible]ong-term treatment.

Animals were tested for withdrawal responding 8h [illegible]reatment with diazepam (i.e. 8h after the 2nd dose on the 7th day). Assessments [illegible]of diazepam acutely were made 45 min after treatment, and to determine the ef[illegible]ong-term treatment with diazepam, animals were tested 45 min after the adminis[illegible]f[illegible]2nd dose of diazepam on the 7th day.

2. The above protocol was repeated using 2.5 mg[illegible]epam and 0.1 and 10 mg/kg AGN 2979. In order to ensure that the withdrawal from Ad[illegible]not associated with delayed problems, separate groups of mice were used to ass[illegible]withdrawal effects 8 hr, 24hr,

48 hr, 96 hr, 144 hr and 10 days after administration of the last dose of AGN 2979.

The results are indicated in the accompanying Figs. 10 to 13 and are discussed below.

Fig. 10 shows the anxiolytic action of 2.5 mg/kg diazepam given acutely or chronically (2.5 mg/kg i.p. given b.d., tested on day 7) and the effects of withdrawal measured 8, 48 and 96 hr after administration of the last dose of diazepam. C indicates the responses of vehicle-treated control animals receiving a single injection of vehicle or those receiving vehicle twice daily for 7 days, P greater than 0.005). n=6. S.E.M.s less than 12.4%. *,+P less than 0.001 (Dunnett's t test).

Fig. 11 shows the anxiolytic action of 10.0 mg/kg diazepam given acutely or chronically (10.0 mg/kg i.p. given b.d., tested on day 7) and the effects of withdrawal measured 8, 48 and 96 hr after administration of the last dose of diazepam. C indicates the responses of vehicle-treated control animals receiving a single injection of vehicle or those receiving vehicle twice daily for 7 days, P greater than 0.05).

n=6. S.E.M.s less than 12.2%. *,+P less than 0·01—P less than 0.001 (Dunnett's t test). ° indicates sedation.

Fig. 12 shows the anxiolytic action of 0.1 mg/kg AGN 2979 given acutely or chronically (0.1 mg/kg i.p. given b.d., tested on day 7) and the effects of withdrawal measured 8, 48 and 96 hr after administration of the last dose of AGN 2979. C indicates the responses of vehicle-treated control animals receiving a single injection of vehicle or those receiving vehicle twice daily for 7 days, P greater than 0.05).

n=6. S.E.M.s less than 11.7%. *,+P less than 0.001 (Dunnett's t test).

Fig. 13 shows the anxiolytic action of 10 mg/kg AGN 2979 given acutely or chronically (10·0 mg/kg i.p. given b.d., tested on day 7) and the effects of withdrawal measured 8, 48 and 96h after administration of the last dose of AGN 2979. C indicates the responses of vehicle-treated control animals receiving a single injection of vehicle or those receiving vehicle twice daily for 7 days, P greater than 0.05).

n=6. S.E.M.s less than 12.1%. *,+P less than 0.001 (Dunnett's t test).

Acute treatment with diazepam, 2.5 mg/kg i.p., caused an anxiolytic response in the mouse test procedure. This was characterised by reduced aversion to the white, brightly-lit area of the test box (rearings and line crossings in the white significantly increased). The increased behavioural responding in the white area was mirrored by reduced behaviour in the black (Fig. 10). This anxiolytic action of diazepam was associated with a prolonged latency for entering the black section of the box, and with a reduced % of time spent in the dark section. In this, as in other experiments reported here, transitions between the two compartments of the test box were not significantly modified by drug treatment.

The anxiolytic action of 2.5 mg/kg i.p. diazepam was maintained on subchronic treatment (Fig. 10). However, when treatment was withdrawn a clear anxiogenesis developed which was characterised by reduced latency to enter the black section of the test box, increased rearings and line crossings in the black, and increased time spent in the black. This anxiogenesis was apparent within 8h of the last treatment with diazepam and persisted for 48 h (Fig. 10).

Similar data was obtained using a higher dose of diazepam, 10 mg/kg i.p. The major differences seen between the high and low dose diazepam treatment was (1) the sedative action of the former which was apparent on acute treatment (tolerance to this sedative action developed within 3 days of continued b.d. treatment), and (2) the more clear persistence of the withdrawal anxiogenesis for 48 hr after ceasing treatment (Fig. 11).

The anxiolytic action of AGN 2979 was seen on acute treatment with 0.1 mg/kg (Fig. 12) and 10 mg/kg (Fig. 13): sedation was not observed. The nature of the anxiolytic action of AGN 2979 was, like diazepam, characterised by a reduced latency to enter the black section of the test box, increased exploratory behaviour in the white (increased rearings and line crossings) with corresponding decreased behaviour in the black (decreased rearings and line crossings), which correlated with a reduced % of time spend in the black during the 5 min test session.

The anxiolytic action of AGN 2979 was maintained on continued b.d. treatment. However, in marked contrast to the findings with diazepam, abrupt cessation of treatment with AGN 2979 was not associated with anxiogenesis. Indeed, in complete contrast, an anxiolytic action was clearly apparent 8h after last dosing with 0.1 mg/kg AGN 2979 and 48 h after last dosing with 10 mg/kg AGN 2979 (Figs. 12 and 13). This anxiolytic action slowly waned over the subsequent 48 h period, and careful observations using separate groups of animals (animals must be naive to the test situation) showed that anxiogenesis did not follow the withdrawal of treatment with AGN 2979, and indeed did not develop at any time during a 10 day period following withdrawal of therapy. It is emphasised that this marked contrast in response of mice following withdrawal from subchronic treatments with diazepam and AGN 2979 is apparent when identical treatment protocols are used.

EXAMPLE 11

Male laboratory bred common marmosets (Callithrix jacchus), weighing between 350–400g,

were housed individually and allowed food (mazuri primate diet S.D.S. Ltd, Essex) 'ad libitum'. Once daily marmosets were also given as assortment of fruit and brown or malt bread. Holding rooms were maintained at 25± 1°C at a humidity of 55% and on a 12 h light/dark (red illumination) cycle (with simulated dawn and twilight periods) with lights on at 07.00 h.

Tests were conducted between 13.30–15.30 h in the normal holding room (to avoid unwanted disruption of behaviour by movement to a novel room or cage). The holding cages, in which marmosets were housed individually for the present work, measured 76 cm high, 50 cm wide and 60 cm deep. "Anxiety' was initiated by a human observer standing 0.6 m in front of the holding cage. Changed behaviour was recorded over a 10 minute period (consecutive 2 minute recordings for each behavioural response were measured) both by the observer and by blind assessment by an independent observer of video recordings taken throughout the period of human threat. The behavioural measures selected for the present studies were (a) % of time spent on the cage front in direct confrontation with the human threat and (b) the number of aggressive body postures, primarily shown as raising of the tail to expose the genital region with varying body piloerection, anal scent marking and slit stare with flattened ear tufts.

The results are indicated in Figs. 14 and 15 and discussed below.

Fig. 14 shows the anxiolytic action of diazepam in the marmoset shown as an increase in the % of time spent on the cage front, and a reduction in the number of postures, when confronted with a human threat standing 0.6 m in front of the holding cage. n=6. S.E.M.s shown or less than 12.2% *,+P less than 0.001 (one-way ANOVA followed by Dunnett's test).

Fig. 15 shows the anxiolytic action of AGN 2979 in the marmoset shown as an increase in the % of time spent on the cage front, and a reduction in the number of postures, when confronted with a human threat standing 0.6 m in front of the holding cage. n=6. S.E.M.s shown. *,+P less than 0.001 (one-way ANOVA followed by Dunnett's test).

Diazepam was administered subcutaneously at doses of 0.1 and 0.025 mg/kg and AGN 2979 was similarly administered at doses of 0.00001, 0.0001, 0.001 and 1 mg/kg.

Marmosets treated with diazepam exhibited a change in behaviour characteristic of treatment with an anxiolytic agent. Thus, they responded to a human threat by spending more time on the cage front in direct confrontation with the experimenter, and they spent less time directing aggressive postures at the experimenter (shown as a reduction in the number of postures). Diazepam was active to reduce anxiety in the marmoset at doses of 0.01 and 0.025 mg/kg s.c. (Fig. 14).

Similarly to diazepam, AGN 2979 was shown to exert anxiolytic activity in the marmoset, seen both as a reduction in the number of postures and an increase in % of time spent on the cage front (Fig. 15). Marmosets treated with AGN 2979 were generally so lacking in fear of the experimenter that they spent considerably more time than control animals jumping backwards and forwards between the cage front and the cage perches, which generally reflects playful behaviour, and this led to an artificial reduction in the % of time spent on the cage front. From the data obtained, there is no indication that AGN 2979 is any less effective than diazepam as an anxiolytic agent in the marmoset AGN 2979 is, however, more potent than diazepam.

The marmoset was found to be particularly sensitive to the sedative actions of diazepam and it was therefore difficult to make behavioural measures on animals treated with doses of diazepam in excess of 0.025 mg/kg. However, sedation was never seen following treatment with AGN 2979.

EXAMPLE 12

The procedure of Example 6 was repeated using 0.01, 0.1, 1 and 10 mg/kg (−)AGN 2979 administered intraperitoncally as a 45 minute pretreatment in a volume of 1ml/100g body weight.

The results are indicated in accompanying Fig. 16 and discussed below.

Fig. 16 shows changes in rearing behaviour and line crossings (locomotion) in the white and black sections of the box. C indicates the responses of vehicle-treated, control animals. n=5. S.E.M.s given. Significant increases in responding are indicated as *P less than 0.001, significant decreases as +P less than 0·001 (one-way ANOVA followed by Dunnett's t test).

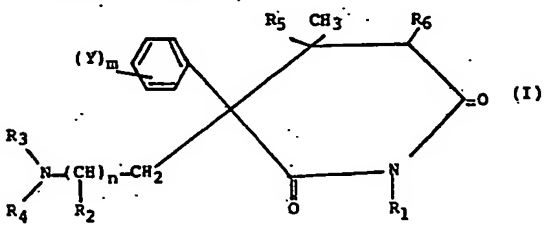
When give intraperitoneally, using a 45 min pretreatment time, the (−)isomer of AGN 2979 was shown to exert marked anxiolytic activity across the dose range 0.01–10 mg/kg. This anxiolytic activity was characterised by increased line crossings and rearing behaviour in the white section of the test box with correspondingly decreased behaviour in the black (Fig. 16). The anxiolytic activity of (−)AGN 2979 was also associated with reduced latency for movement from the white to the black section of the test box (normal control values in the range 7–12 seconds, this was delayed at all doses of (−)AGN 2979 to 16–59 seconds, P less than 0.01–P less than 0.001), and decreased time spent in the black (normal values in the range 51–54%, reduced to 19–39% at all doses of (−)AGN 2979, but with the reduction being most marked at the higher doses, P less than 0.001).

The results indicate that (−)AGN 2979 is more potent as an anxiolytic agent than (±)AGN

2979:

CLAIMS

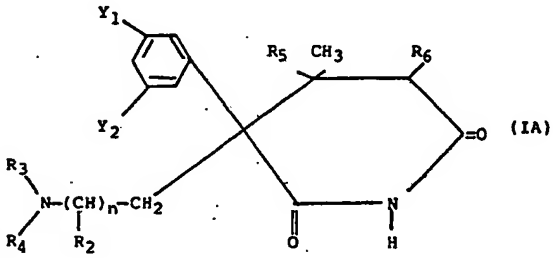
1. A pharmaceutical composition in unit dose form comprising, with a pharmaceutically acceptable diluent or carrier, an amount of 10^{-7} to 10^{-1} mg per unit dose of compound of the following Formula I.



(I)

wherein:
R_1 represents hydrogen or C_1–C_4 alkyl;
n is 1 or 2;
R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;
R_3 represents hydrogen or C_1–C_2 alkyl;
R_4 represents C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl;
m is 0 to 3; and
each Y is in a meta or para position and independently represents hydroxy, C_1–C_2 alkoxy, C_1–C_2 alkyl, C_1–C_2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,
or a pharmacologically acceptable salt thereof.

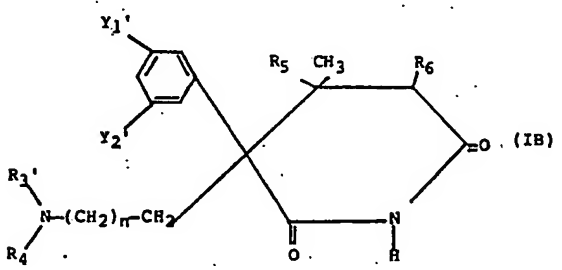
2. A composition as claimed in Claim 1, wherein the compound has the following Formula IA.



(IA)

wherein:
n is 1 or 2;
R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;
R_3 represents hydrogen or C_1–C_2 alkyl;
R_4 represents C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl; and
Y_1 and Y_2 independently represent hydrogen, hydroxy or C_1–C_2 alkoxy,
or a pharmacologically acceptable salt thereof.

3. A composition as claimed in Claim 2, wherein the compound has the following Formula IB.



(IB)

wherein:
n is 1 or 2;

R_3' and R_4 independently represent C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl; and
Y_1 and Y_2 independently represent hydrogen, hydroxy or C_1–C_2 alkoxy,
or a pharmacologically acceptable salt thereof.

4. A composition as claimed in Claim 3, wherein Y_1' represents hydroxy or methoxy and Y_2' represents hydrogen, hydroxy or methoxy.

5. A composition as claimed in Claim 3 or Claim 4, wherein Y_2' represents hydrogen.

6. A composition as claimed in any one of the preceding claims, wherein R_3 and R_4 both represent methyl.

7. A composition as claimed in any one of the preceding claims, wherein *n* is 2.

8. A composition as claimed in Claim 5, wherein Y_1' represents hydroxy or methoxy, R_3 and R_4 both represent methyl and *n* is 2.

9. A composition as claimed in any one of the preceding claims, wherein R_5 represents methyl and R_6 represents hydrogen.

10. A composition as claimed in Claim 3, wherein the compound is 3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dixopiperidine.

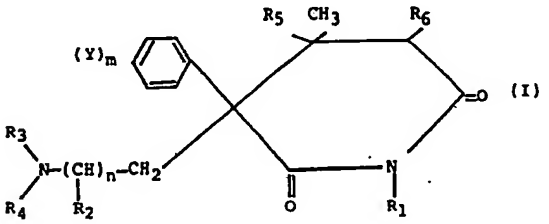
11. A composition as claimed in Claim 10 wherein the compound is the minus isomer.

12. A composition as claimed in Claim 3, wherein the compound is 3-(3'hydroxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine.

13. A composition as claimed in any one of the preceding claims, which contains 10^{-5} to 10^{-1} mg of the said compound of Formula I.

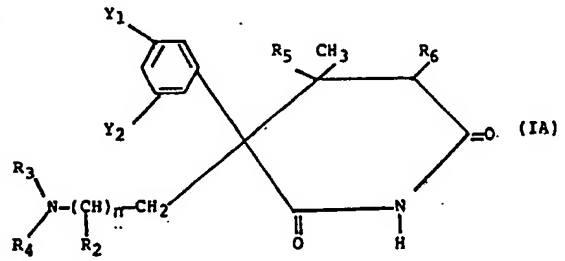
14. A composition as claimed in Claim 14 which contains 10^{-4} to 10^{-1} mg of the said compound of Formula I.

15. The use as an anxiolytic agent in the manufacture of a medicament for the treatment of anxiety of a compound of the following Formula I.



wherein:
R_1 represents hydrogen or C_1–C_4 alkyl;
n is 1 or 2;
R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when n is 2;
R_3 represents hydrogen or C_1–C_2 alkyl;
R_4 represents C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl;
m is 0 to 3; and
each Y is in a meta or para position and independently represents hydroxy, C_1–C_2 alkoxy, C_1–C_2 alkyl, C_1–C_2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,
or a pharmacologically acceptable salt thereof.

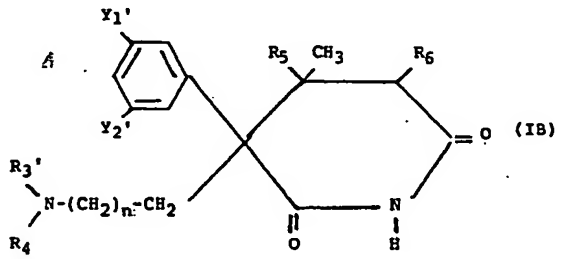
16. A use as claimed in Claim 15, wherein the compound has the following Formula IA.



wherein:
n is 1 or 2;
R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when *n* is 2;
R_3 represents hydrogen or C_1–C_2 alkyl;
R_4 represents C_1–C_2 alkyl;

R_5 and R_6 independently represent hydrogen or methyl; and
Y_1 and Y_2 independently represent hydrogen, hydroxy or C_1–C_2 alkoxy,
or a pharmacologically acceptable salt thereof.

17. A use as claimed in Claim 16, wherein the compound has the following Formula IB.



(IB)

wherein:
n is 1 or 2;
R_3' and R_4 independently represent C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl;
Y_1' represents hydroxy or C_1–C_2 alkoxy; and
Y_2' represents hydrogen, hydroxy or C_1–C_2 alkoxy,
or a pharmacologically acceptable salt thereof.

18. A use as claimed in Claim 17, wherein Y_1' represents hydroxy or methoxy and y_2' represents hydrogen, hydroxy or methoxy.

19. A use as claimed in Claim 17 or Claim 18, wherein Y_2' represents hydrogen.

20. A use as claimed in any one of Claims 15 to 19, wherein R_3 and R_4 both represent methyl.

21. A use as claimed in any one of Claims 15 to 20, wherein *n* is 2.

22. A use as claimed in Claim 19, wherein Y_1' represents hydroxy or methoxy, R_3 and R_4 both represent methyl and *n* is 2.

23. A use as claimed in any one of Claims 15 to 22, wherein R_5 represents methyl and R_6 represents hydrogen.

24. A use as claimed in Claim 17, wherein the compound is 3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dixopiperidine.

25. A use as claimed in Claim 24, wherein the compound is the minus isomer.

26. A use as claimed in Claim 17, wherein the compound is 3-(3'hydroxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine.

27. A use as claimed in any one of Claims 15 to 26, wherein the medicament is in unit dosage form and contains 10^{-7} to 10^{-1} mg of the said compound of Formula I.

28. A use as claimed in any Claim 27, wherein the medicament is in unit dosage form and contains 10^{-5} to 10^{-1} mg of the said compound of Formula I.

29. A use as claimed in Claim 28, wherein the medicament is in unit dosage form and contains 10^{-4} to 10^{-1} mg of the said compound of Formula I.

30. A composition as claimed in Claim 1 and substantially as hereinbefore described.

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